The Role and Essence of Pilot Trials and Subgroup Analysis in Cardiovascular Research: The IMPI Trial Experience

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Thesis Abstract

Background

Randomised control trials (RCTs) are capital-intensive projects and demand substantial human and capital resources. Therefore, proper planning, precise research questions and adequate thoughts are required in areas such as acceptability of the intervention, participant recruitment, and selection of measurable outcomes. Ensuring all these are possible before delving into the main work can be forecasted through pilot trials. They help in determining the feasibility of the intended critical endpoints and ensure the applicability of the result findings. However, no matter how noble and vital the results are, improper reporting can make them unusable.

The thesis brings to the fore the importance of pilot trials in low- and medium-income countries and how they can help make a case for more extensive definitive trials. It then focuses on how subgroup analysis can be used as an essential statistical tool for fully understanding clinical trial results and can be used to unearth non-apparent results in RCT. In the thesis, we highlight the need for accurate, systematic and complete reporting of pilot trials, by critically appraising the literature on abstract reporting in heart failure. The thesis discusses several aspects of pilot trial processes to understand better its unique role in helping refine the components of RCT, to make the running smooth and findings affirmative. Leveraging on the experience of working as a clinical research fellow in the second Investigation for Management of Pericarditis in Africa (IMPI-2) trial, the lessons learnt in planning, designing, implementation, recruitment and reporting of the IMPI-2 pilot forms the nucleus of this thesis. The experience acquired in the process and how they can help in planning future definitive studies are discussed in different sections of the thesis.

Methodology

The thesis uses the experience gained in critical appraisal of the literature, participation in preliminary planning and active participation in a multicentre randomised control trial to understand the importance of some issues during an RCT. These areas include the need for specific objective setting, identification of research participants and collaborators, the acceptability of research intervention, proper identification of possible outcome measures, retention of participants and quality reporting of research findings.

It begins with an overview of pilot trials, subgroup analysis and tuberculous pericarditis which is the primary disease focus of the IMPI project. Each subsequent chapter of the thesis is presented either as a published manuscript or prepared for submission as a manuscript.

The quality of reporting of pilot trials is then examined by systematically surveying the reporting of abstracts of pilot trials in heart failure using the checklist of the Consolidated standard for reporting of trials (CONSORT) extension for pilot trials. A subgroup analysis of IMPI-1 trial planned a priori on the modification of the effect of prednisolone by baseline pericardiocentesis status of trial participants is used to highlight the role subgroup analysis can play in unmasking the group effect in the randomised control trial. The thesis then goes on to present the preliminary report of the IMPI-2 pilot study, highlighting the lessons learned and aspirations in need of refining.

Retention of study participants is essential to achieve success in clinical trials, one way of ensuring this is by letting the study participants understand the objectives and processes of the research and gaining their confidence. Thus, in chapter six, we piloted the use of the University of California San Diego Brief Assessment of Capacity to Consent (UBACC), a screening tool for evaluation of informed consent (IC) comprehension as a training tool for iterative learning and evaluation of consent comprehension among IMPI-2 pilot trial participants.

Results and Conclusion

Enormous resources expended in clinical research can yield good returns before the main work commences, a well-planned micro trial run in the form of a pilot study is undertaken. Our systematic survey of abstracts of pilot trials in heart failure showed that reporting of abstracts of pilot trials is currently suboptimal. Deciding ahead of time on what to report by systematically identifying the different sections needed to inform the audience can improve the quality adequately. Planning subgroup analysis during the design of main studies can help reveal unsuspected findings. The subgroup analysis result showed that pericardiocentesis, despite its essential use among patients with pericardial effusion, did not significantly influence the effect of prednisolone on the primary critical outcomes among IMPI-1 participants. The preliminary report of IMPI-2 trial was designed as a two-phase study; phase 1 results showed that at 50mg, intrapericardial alteplase was safe in facilitating complete pericardiocentesis, while phase two showed that it was feasible to recruit, randomised and follow up patients in line with the study protocol. However, we identified participant retention as a considerable challenge. The result of the pilot revealed that more effort should be expended on participants' education on the clinical condition, the reason for the trial and the need for follow-up adherence. There is also a need to make adequate provision for the use of field workers for contact tracing to reduce the dropout rate. In the main trial protocol, there may also be a need to reconsider the patient's selection and use of fibrinolysis in malignant effusion, judging from the high rate of 3 months mortality in this group of patients.

The results of the informed consent study showed that an improved level of comprehension followed the use of iterative learning, a higher level of education and non-use of interpreters during informed consent delivery. These finding led us to conclude that every effort should be made to ensure that research participants entirely buy into the research they are asked to be

part of through thorough information delivery. Doing so can help improve participants adherence to the trial follow-up.

Overview of The Thesis

In this PhD thesis I set out to achieve the following:

1. Critically appraise the literature on pilot trials, subgroup analysis and tuberculous pericarditis - the building blocks for the works for the research
2. Systematically evaluate the quality of pilot trial reporting by focusing on heart failure pilot trials and, in that process, get familiar with the crucial items in reporting of pilot trials. Complete itemised reporting can help avoid missing out any detail and, ultimately, improve the conduct of the definitive main study. The exercise is part of the preliminary preparations for reporting of the findings of the second investigation of management of pericarditis in Africa (IMPI-2) pilot trial.
3. Understand how to conduct, analyse and report subgroup studies in RCT and, by so doing, show how subgroup analysis can further reveal RCT results.
4. Report the two-phase IMPI-2 preliminary study comprising of dose-finding (*Phase 1*) and IMPI-2 feasibility study (*Phase 2*) in preparation for the main trial and use the report to practically implement concepts already discussed in the introduction.
5. Present a pilot report of a tool for informed consent comprehension and show how this can help us improve participant adherence in the main trial.
6. Describe how piloting, subgroup analysis and the strategies outlined in 1-5 above can be used collectively to the improve the efficacy and yield of clinical trials using the IMPI trials as a reference example
7. Through use of different research methodologies in the chapters, the thesis to explored pilot trial designs and subgroup analysis for randomized clinical trials. The experience of the investigation for management of pericarditis (IMPI) trial is used in understanding how to improve the conduct and report of RCT.

In many resource-limited environments such as sub-Saharan Africa, the funding, infrastructure and resources required to invest in the conduct of large randomised controlled studies and other resource-intensive clinical studies are often not available. Researchers in these regions, therefore, find it difficult to conduct such studies and, when they do, several limitations make their results non-generalizable. Two essential research tools which are underutilised to aid and facilitate research and address important questions are pilot trial and subgroup analyses of randomised controlled studies. Used efficiently they have the potential through their findings to provide the rationale for the conduct of larger more capital-intensive studies, train human resources and attract collaborators for bigger works, as well as boost funders' confidence in the ability of the sites for more extensive studies.

Pilot trials allow clinician/researchers the opportunity, to test the feasibility of conducting clinical trials; to test the safety of the investigational product and conducting the study; to identify protocol related factors that make the study work or not work and, more importantly, to recognize items and issues that can or cannot be modified.

Subgroup analyses of already conducted randomised controlled studies are another critical, efficient and effective mechanism for answering important clinically relevant questions, especially where resources and capacity to conduct studies are not available. However, for the information from sub studies to be meaningful and useable, there is a need to have a clear understanding of the strengths and weaknesses of substudies, when they are indicated and acceptable methodological approaches to conducting them.

The thesis provides an in-depth examination and exploration of the role of pilot trials in a resource-limited environment by using literature review, critical appraisal of the literature and practical example of a pilot trial which the researcher contributed to its design and conduct. In doing this, the focus is laid on the pilot trial protocol development, abstract publication and ability to inform the successful design and conduct of a more extensive study. In the thesis,

we also provide a practical example of a subgroup analysis from a randomised controlled study designed to help address an important clinical question which may influence clinical practice and patient outcomes.

Chapter one is made up of introduction and review of the literature designed to summarize the following essential topics, all of which are core to the thesis and its objectives: i) Pilot Trials; ii) Subgroup analyses; iii) Tuberculous pericarditis, its management and outcomes; iv) The IMPI trial experience v) Informed consent comprehension and tools to improve the process.

Chapter two is a protocol for critical appraisal of the quality of pilot trial, published as a way of illustrating the importance of high-quality protocols, to informing the subsequent design and development of modifiable methods of conducting a larger trial.

Chapter three is a published critical appraisal of the quality of abstracts of pilot trials using heart failure related studies as the subject of focus and a systematic survey as the methods. In the survey, 92 out of 228 retrieved publications met the inclusion criteria. Pharmacological interventions were associated with better reporting. However, the overall quality of reporting of abstract, based on the Consolidated Standard for Reporting of Trials (CONSORT) extension for reporting of abstract of pilot trials, was suboptimal.

Chapter 4 addresses a subgroup analysis of the IMPI-I trial. In it, we evaluate whether the effectiveness of adjunctive steroid therapy on the primary composite outcome of the trial is modified in the subgroup of patients who have had pericardiocentesis before the use of steroids. The analysis illustrates how subgroup analyses when performed and used correctly can be a useful tool to answer important questions, without having to repeat expensive large trials, to understand the limitations to the interpretations drawn from the conclusions.

Chapter 5 was designed as a two-phased study (a dose-finding study and a feasibility study). In it, we present a practical example of the use of a pilot trial to inform the design and conduct

of a larger trial on patients presenting with large pericardial effusion. It is on the use of tissue plasminogen activator, compared with conventional pericardiocentesis to reduce combined primary outcome of death, repeat effusion with tamponade and pericardial constriction. The results show that the use of 50mg of alteplase is safe in facilitating complete drainage and recruitment is feasible. However, the high dropout rate in the pilot demands modification of protocol to ensure adequate follow-up. One way to address this is the focus of the next chapter of the thesis.

In Chapter 6 we show that informed consent comprehension is key to ensuring autonomy and confidence of study participants. This chapter presents the results of a feasibility study on the use of University of California San Diego Brief assessment of capacity to consent Questionnaire (UBACC) as a training tool to improve consent comprehension among participants of the IMPI-2 pilot trial. The results of the study may allow for the implementation of an informed consent process that ensures better participant comprehension.

In the 7th and final chapter, we present a summary and discussion of the major conclusions from the thesis, lessons learned, limitations and the essential take-home messages of the role of pilot trials and subgroup analyses to answer clinically relevant questions in resource-limited and other environments.

Acknowledgements

My deepest gratitude goes to God the fountain of all wisdom for his grace and sustenance throughout this study.

I wish to begin with a posthumous thank you to the late Prof Bongani Mayosi, my initial supervisor, who laid the foundation for this research and the forbearer of the IMPI project. I am grateful for all his support. Encouragement and for his contagious enthusiasm even amidst personal challenges. I especially thank him for introducing me to another mentor, father and supervisor par excellence, Prof Lehana Thabane, who took it upon himself to ensure that I climbed the heights standing on his shoulders and taught me a lot in so short a time.

I appreciate the sacrifice of Prof. Mpiko Ntsekhe for picking up the reigns as my supervisor following the untimely passing of Prof Mayosi, despite his already very busy schedule; I also cannot thank Prof Karen Sliwa enough for her support and encouragement at the time it mattered most in providing supervision and confidence.

Associate Prof. Jantina De Vries played a prominent role in seeing this endeavour to fruition, and I am indebted to her kindness, as well as to the assistance of Dr Freedom Gumedze of statistical sciences department UCT. I wish also to acknowledge the support of the head of department of Medicine, University of Cape Town, Professor Ntobeko Ntusi.

My appreciation also goes to the entire IMPI-2 trial team for allowing me to share in the experience; the memory will last a lifetime. I especially thank my research nurse, Sr Una Seas, to whom I owe a debt of gratitude, as well as the trial coordinator, Sr Veronica Francis, the data manager, Ms Shaheema Pandie, as well as Lwazi, Sr September and Felicia. The assistance of the staff of Groote Schuur hospital cardiac catheterization laboratory especially Drs Shahen Pandie, Chishala Chishala, Arthur Mutyaba and nursing staff is acknowledged.

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Finally, I wish to express my profound gratitude to my siblings Dee Stella, Comfort and Chioma, my lovely wife Gladys and children Munachiso, Nmesoma, Kosisochukwu and Chimdaalu for bearing with my absence and for keeping the home front. I love you all.

Publications and Statement on My Contributions to the Study

The thesis contains published articles in peer review journals and prepared manuscript for submission as listed below:

Published articles

1. G. Isiguzo, M. Zunza, M. Chirehwa, B.M. Mayosi, L. Thabane, Quality of abstracts of pilot trials in heart failure: A protocol for a systematic survey, *Contemporary Clinical Trials Communications* (2017), doi: 10.1016/j.conctc.2017.11.004

   The contribution of the candidate: responsible for development and refining of the concept, the identification of co-reviewers, development of data extraction tool, literature search, selection of eligible manuscripts for the survey and drafting and editing of the manuscript for publication.

2. Isiguzo GC, Zunza M, Chirehwa M, Mayosi BM, Thabane L. Quality of pilot trial abstracts in heart failure is suboptimal: a systematic survey. Pilot and Feasibility Studies. 2018;4(1):107.

   Contributions of the candidate: data extraction, paper reviews, manuscript development, implementation and incorporation of co-authors inputs. Also responsible for the production of the final edition of article publication.

3. GC. Isiguzo, L. Thabane, MA. Familusi, K. Sliwa, M Ntsekhe, J. De Vries. Piloting a Tool for Informed Consent Comprehension in a Cardiovascular Clinical Trial in South Africa: An IMPI-2 Pilot Trial Substudy. South African Medical Journal (Accepted for publication).

Contributions of the candidate: Development of the concept, data collection and drafting of manuscript for publication.

Unpublished Articles for submission

1. GC. Isiguzo, L. Thabane, F Gumedze, K. Sliwa, M Ntsekhe. The impact of pericardiocentesis on the effectiveness of adjuvant corticosteroids in Tuberculous Pericarditis: An IMPI-1 Trial Subgroup Analysis
2. GC. Isiguzo, K. Sliwa, V. Francs, L. Thabane, M Ntsekhe. Complete percutaneous pericardial drainage facilitated by intrapericardial alteplase compared to conventional routine care when indicated in adults with large pericardial effusion: Preliminary Report of a Pilot Randomized Control Trial.

I worked as a clinical research fellow in the IMPI-2 trial. Together with the principal investigators, co-investigators, trial coordinator, data managers, research nurses, I contributed to the development of the IMPI-2 trial protocol, informed consent forms, case report forms, data collection tools and database.

Part of the work presented in this thesis was a collaborative effort made possible by the 'IMPI warrior' team as our mentor and beacon, the late Prof Bongani Mayosi, liked to address us. I joined this team as a clinical research fellow, and my contributions can be viewed from three angles: as a clinician, as part of the administration and in trial advocacy.

My clinical duties started from the second patient enrolled in the dose-finding study to the pilot trial. It included screening the patients for eligibility, conducting 2D echocardiography, enrolment, pericardiocentesis and trial procedures. I did this with the able assistance of the cardiology fellows, IMPI-2 research nurses, and Groote Schuur Hospital Cath lab staff.

Together with the principal investigators, co-investigators, trial coordinator, research nurses, data managers, we held weekly meetings to develop the case report forms, study research

protocol, database development, data collection tools, the definition of study outcomes and report writing.

I made presentations to the doctors in different referring hospitals and with the medical and emergency ward staff to raise awareness concerning the IMPI-2 trials and answered questions they had concerning the trial and patients' care. I also made bi-weekly telephone calls, followed up with monthly emails, often to remind selected Physicians of the trial. Together with the research nurse I also called patients from time to time to remind them of the follow-up appointment and to take their questions whenever the need arose.

Finally, the research journey presented in the pages of this thesis sums up the need to start small and simple while dreaming big.

I wish to confirm that this thesis is an original research and that I was the lead author for the listed publications. The manuscripts were developed under careful guidance of my supervisors. All authors contributed to the preparation of the scripts and gave final approval for their submission. Details of my specific contributions are presented under the introduction of each.

Plagiarism Declaration

The contents of the thesis are my work and are not copied from anywhere (published or unpublished). None of the materials have been submitted in any form at UCT or elsewhere for assessment.

List of Abbreviations

ADA	Adenine dinucleotide
AIDS	Acquired immune deficiency syndrome
ARV	Anti-retroviral
BICEPS	Brief informed consent evaluation protocols
CD4	Cluster of differentiation 4
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report forms
CT	Computerised tomography
CVD	Cardiovascular disease
DLT	Dose limiting toxicity
DICCT	Deaconess Informed Consent Comprehension Test
DICCQ	Digitised Informed Consent Comprehension Questionnaire
DNA	Deoxyribonucleic acid
DST	Drug sensitivity testing
DSMB	Data safety monitoring board
ELISPOT	Enzyme-linked immunospot
EPTB	Extrapulmonary tuberculosis
ESR	Erythrocyte sedimentation rate
HIV	Human immunodeficiency virus

HREC	Human Research Ethics Committee
IA	Intrapericardial alteplase
IC	Inform Consent
ICC	Informed Consent Comprehension
IFN-γ	Interferon gamma
IMPI	Investigation of the Management of Pericarditis in Africa
IQR	Inter quartile range
IRR	Incidence Risk Ration
IVC	Inferior Vena Cava
LA	Left Atrium
LMICs	Low- and Medium-Income Countries
LV	Left ventricle
MeSH	Medical Subject Heading
MDG	Millennium Development Goals
MDRTB	Multi Drug Resistant Tuberculosis
MIC	Minimum Inhibitory Concentration
MRI	Magnetic resonance imaging
MTB/RIF	Mycobacterium Tuberculosis/ Rifampicin Sensitivity Testing
MTD	Maximum Tolerated Dose
NSAIDS	Non-Steroidal Anti-inflammatory Drugs
NYHA	New York Heart Association
OR	Odd Ratio
PE	Pericardial Effusion
PROSPERO	Prospective Register of Systematic Reviews

PRISMA-P	Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
QuIC	Quality of Informed Consent Test
RCT	Randomise Control Trial
RV	Right Ventricle
SAMRC	South African Medical Research Council
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TB	Tuberculosis
TBP	Tuberculosis Pericarditis
TGF-β_1	Transforming Growth Factor beta-1
TH-1	Type 1 T-helper Cells
TH-2	Type 2 T-helper Cells
t-PA	Tissue Plasminogen Activator
UBACC	University of California San Diego Brief Capacity to Consent
WHO	World Health Organization

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Chapter 1: Introduction and Literature Review

1.1 General Comments

Randomised control trials (RCTs) are a vital source of evidence that shape clinical practice. Proper planning and preparations go into the conduct of RCTs for them to effectively play this role. Pilot studies provide essential building blocks for RCTs by serving as “crystal balls” to peep into the processes of main studies and help prepare the team ahead of time.

The first investigation of pericarditis (IMPI-1) trial, a randomised control trial on the use of adjunctive steroids and immunotherapy raised discussions on how the use of these interventions affect short term complications such as tamponade requiring pericardiocentesis, hospitalisation, and long-term complications such as the risk of malignancy, death and constrictive pericarditis. The main conclusion from the trial was that adjunctive steroid and immunotherapy did not have any effect on the primary composite outcome of all-cause mortality, tamponade requiring pericardiocentesis and pericardiocentesis; they also led to increased incidence of HIV-related malignancy. Use of prednisolone resulted in a reduction of secondary outcomes of hospitalisation and constrictive pericarditis. However, these IMPI-1 trial conclusions were based on the entire study population; there is a need to examine further their consistency through evaluation of the robustness of the overall results and seeing how the intervention effects differed based on individual population characteristics. In IMPI-1, provision was made for this interrogation of the RCT results through a priori subgroup analysis to explore if there was any difference in the effects among the subgroups; one such subgroup was pericardiocentesis status at baseline.

In the second investigation for management of pericarditis (IMPI-2) trial, percutaneous drainage facilitated by intrapericardial fibrinolysis will be compared with routine pericardiocentesis, so the lessons from this subgroup analysis on the influence of pericardiocentesis will aid our understanding of the results of the RCT better. It will also contribute to the planning of the pilot trial and ultimately the next phase of the IMPI study.

The experience garnered in understanding the different research methods involved in the IMPI trial and using the knowledge in planning the execution of the current phase of the trial form the crux of this thesis.

1.2 Pilot trials, their roles in directing clinical research

1.2.1 Definition

Pilot trials refer to small preliminary studies which aid researchers in deciding on starting larger confirmatory trials (Arain et al. 2010a; Conn et al. 2010; Thabane et al. 2010) They are made up of a distinctive group of randomised controlled trials which are often referred to as pilot or feasibility studies, which do not have effectiveness or efficacy as their primary focus (Eldridge et al. 2016). They are a version of the main study run in miniature form to determine if the components of the main study can work (Glossary 2013). Pilot trials are not by nature designed for testing of hypothesis but rather should emphasise confidence interval estimation (Lancaster 2015; Lancaster, Dodd, and Williamson 2004a) and are usually set up to support the development of a future definitive RCT (Anderson and Prentice 1999).

Pilot trials in their design are used to lay the foundation for a larger trial. They provide information for planning and justification of randomised control trials and often, their results can lead to changing of study design (Arain et al. 2010a). They are usually focused on ensuring of the smooth running of the processes in the main study such as recruitment,

randomisation, treatment, flow and follow up assessment (Leon, Davis, and Kraemer 2011; Ross-McGill et al. 2000).

Pilot trials are a form of a feasibility study in that they test the feasibility of conducting the main trial (Whitehead, Sully, and Campbell 2014; Thabane et al. 2010). They provide training and experience in the running of the main study by highlighting identified problems so that they can be corrected before the main research begins. To distinguish pilot trials from pilot works or pilot studies, one paper referred to pilot trials as stand-alone pilot studies incorporating a randomisation procedure (Arnold et al. 2009).

1.2.2 Features of Pilot trial

For a study to qualify to be designated as a pilot trial, such a study must have a strict study methodology, such as sample size justification and a clear intention for further work must be stated up front. There should be clear understanding that it is a small version of the main study with aspects such as randomisation and use of control as is expected in the main work. Also, the intention should be a focus on the trial process rather than outcome. Since pilot trials mimic main studies, the sample size should be representative of the target population for the main study and should aid the assessment of feasibility by having an adequate sample to provide such information. A pilot trial must also, among other things, be clear on the criteria for success based on the feasibility objectives. These attributes are essential as they serve as a check to lead investigators and reviewers on the four broad feasibility outcomes/conclusions of every pilot trials which are: stop (main study not feasible), continue but modify protocol, continue without protocol modification but monitor process firmly and continue without change (Thabane et al. 2010).

A well-structured pilot trial is made up of certain critical elements such as sample size calculation, the integrity of study protocol, testing of data collection tool/questionnaire, identification of source of participants, procedure involved in randomisation, processes such as recruitment and consent, how acceptable is the intended intervention and ensuring the most appropriate primary outcome measures are selected. These key elements have been referred to as reasons for the pilot trial and grouped into four broad sections, namely; process, resources, management and scientific bases (Van Teijlingen et al. 2001; Van Teijlingen and Hundley 2001). Before commencing a clinical trial, advance estimation is necessary on three classes of parameters. These issues involve administration, process and effect of the treatment; pilot trials address the first two adequately (Wittes and Brittain 1990). The administrative readiness is evaluated by such parameters as the number of participants expected to be identified, the willingness of these participants and their physicians to be part of the trial, and the rate of recruitment, randomization, compliance with the protocol as well as ability to identify events of interest and follow-up related to the process. The dose-finding phase constitutes the scientific bases of the trial hypothesis. It evaluates the dose and safety of the study medicine. Some argue that though it is part of the feasibility, it may not strictly be part of the pilot as already described (Lawrence Gould 2005).

1.2.3 Goals of Pilot trial

Pilot trials, as already defined, guide the planning of larger trials, they assess the safety of interventions, recruitment potentials, the feasibility of international collaboration, multisite coordination, increase experience with study drugs, evaluation of data collection tools and surrogate markers (Leon, Davis, and Kraemer 2011). These various aspects test the preparedness of the study team for the main trial and boast funders' confidence in approving funds for the main study.

Through conducting a pilot trial, an opportunity is created to formulate consistent practice that can enhance data integrity and human subject protection (Leon, Davis, and Kraemer 2011). Pilots are focussed on the process of the main study such as recruitment, randomisation and follow-up. If data from the pilot phase contributes to the final analysis, this is termed internal pilot; however, if it is set aside and not included in the main trial data, it is called external pilot. The pilot phase is usually used in an internal pilot to describe the initial phase in the protocol. In such instances, the investigator estimates the parameters of interest at the end of the pilot and recalculates the sample size (Wittes and Brittain 1990). All observations are treated as if they come from a single study during data analysis at the end of the trial.

A pilot trial could be critical in the training of research personnel through the provision of needed experience, thereby strengthening the competencies and skills needed for conducting the investigation with accuracy and precision (Whitehead, Sully, and Campbell 2014). It can function as a test (and if successful a safeguard) for the investigators and grant agencies to ensure that a future trial is designed optimally and can be implemented in practice (Arnold et al. 2009). It can also provide an opportunity to apply and examine the feasibility of an adverse event reporting system (Leon, Davis, and Kraemer 2011).

1.2.4 Analysis of Pilot Trial

A descriptive analysis should be used for pilot studies, with an emphasis on confidence interval estimation (Burrows et al. 2001) because hypothesis testing requires a power sample size calculation which is usually not available in the pilot. There are instances where the pilot trial has been used to generate sample size calculation (Thabane et al. 2010); however, the use of pilot trial in estimating treatment effect can be biased because of the limited sample size. In

such a situation, caution needs to be applied as a pilot trial can potentially mislead sample size or power calculation (Kraemer et al. 2006).

External pilots which are stand-alone studies, however, can be hypothesis testing driven, but the interpretation of this should be cautious and the results treated as preliminary (Stevinson and Ernst 2000; Whitehead, Sully, and Campbell 2014). Safety efficacy and effectiveness are not evaluated in pilot trials. The temptation not to proceed with main studies when significant differences are found should be avoided.

1.2.5 Limitations of Pilot trial

Janet Wittes, in her paper on the role of internal pilot trials in increasing efficiency of clinical trials (Wittes and Brittain 1990), recounted the teaching of WG Cochran in which he listed pilot trials among undesirable practices; describing the proponents of pilots as mischief makers and concluding that pilots often lead to regret. According to WG Cochrane, when pilots show statistically or nearly significant results, the treatment effect could prevent one from embarking on a large-scale study, as administrators could ask, ‘Why should you perform a large study when a small one sufficed? A small study would not be persuasive enough to influence medical practice.' Whereas a pilot study that showed no effect would also prevent one from initiating a large study because the administrator would challenge, ‘Why should you embark on a major investigation when the pilot did not appear promising?' According to Cochrane, "The power of such a small pilot would be too low to exclude even significant differences among treatments" (Wittes and Brittain 1990).

This opinion is still held by some publishers who insist that most pilot trials rarely act as precursors to bigger studies, while other journals discourage publishing of pilot studies because they consider them less rigorous compared to main studies (Arain et al. 2010a). The

only way pilot trials can break these stereotypes and lead to progression to definitive trials is by having clear methodological rigours.

Inadequate publicity due to poor methodological approach is, therefore, a significant drawback for pilot trials. Though pilots could be used in sample size calculation, however, as already stated, they should not be used to estimate treatment effect due to their limited sample size. Doing so has the potential to mislead sample power calculation for the main study. Labelling studies as a pilot for the wrong reason is another major drawback - identified reasons for doing this may include lack of funding, editor's suggestion, and single-site study (Thabane et al. 2010). Finally, the perception of some publishers and journal editors is another limitation to pilot trials.

1.2.6 How should Pilot trials be reported?

Every research endeavour merit being communicated to the reading public to achieve the desired impact, which is knowledge dissemination leading to change in practice. Pilot trials, by their small and exploratory nature, run the risk of non-reporting especially following negative results. Some publishers, as a policy, do not publish pilot trials claiming that they lack methodological rigor. However, if pilot trials are to fulfil their role of informing the processes and development of larger trials, then efforts should be expended in systematically reporting them. Doing so will discourage repeat of the same errors, as well as help in the planning of main trials. The Consolidated Standard for Reporting of Trials (CONSORT) was developed in 1996 to bring uniformity in ways RCTs are reported (Hopewell et al.). The CONSORT extension for reporting of pilot trials was released in 2016 to include pilot trials reporting. It is a good guide on things to include in the report of pilot trials. Journals can insist that publications

adhere to the use of such tools as included in the CONSORT checklist to improve the completeness reporting of pilot trials (Eldridge S 2016).

In the IMPI-2 trial, certain key features of the CONSORT extension for pilots were added to address pilot trial. These included emphasising to the patients that the major objective was feasibility, stating prespecified parameters to assess success of the objectives, and clearly having prespecified criteria used to judge whether, or how, to proceed with future definitive trial. The randomization technique was also perfected in this internal pilot as we plan to use it in the main trial. In accordance with the CONSORT extension, the findings of the pilot are presented in this thesis as stipulated by guideline.

1.3 The role of subgroup analysis in clinical research: An overview

1.3.1 Introduction

Randomised control trials are usually set up to determine the benefits and harm of interventions but are not powered enough to detect heterogeneity (Collins 1996). The magnitude of these benefits or harm is often dependent on the baseline characteristics of the individual participant. Subgroup analysis is used to investigate the consistency of these treatment effects across groups to ensure correct interpretation and to avoid attributing such importance to heterogeneity in treatment which could have been by chance.

Subgroup analysis can, therefore, be defined as an analysis that explores whether intervention effects (experimental versus control) differ according to the participant's characteristics (Kasenda et al. 2014). They investigate the consistency of heterogeneity of treatment effects across the group based on baseline characteristics, bearing in mind that the observed heterogeneity in treatment effect can arise by chance due to the partitioning of the population. It, therefore, in ensuring that the broad range of effects of intervention in a trial is captured,

plays an essential role in the interpretation of clinical trial findings. Relative risk, odds ratio or arithmetic difference is used to estimate the treatment effect [a comparison between treatment groups] (Wang et al. 2007).

Evaluation of consistency of the trial conclusions among the different population, as defined by each baseline characteristic, is the reason for undertaking subgroup analysis (Wang et al. 2007). The result of RCTs are often complex and made up of pulled results which often are based on several generalizations. Subgroup analysis are used to unpack these results by focusing on group characteristics. By doing this, they may help draw attention to previously unacknowledged findings. However, inappropriate subgroup analysis not supported by scientific rationale can give rise to over-stated and spurious misleading results either by coincidence (multiple testing effect) or by unintended patient selection mechanism (Yusuf et al. 1991; Assmann et al. 2000; Sleight 2000; Lagakos 2006). These situations are rife in post hoc subgroup analysis (where the intention only come after the data is inspected) and such concerns are justified (Alosh et al. 2017). However, there are numerous instances where subgroup analysis has led to discoveries of a new treatment or revising of initial recommendations based on general population results due to the finding out of the beneficial effect of treatment in specific subgroups (Rédei 2008; Bachynsky, Infeld, and Shah 2008).

Subgroup analysis can be categorised into (1) exploratory in cases where the overall effect is not established in the whole study population, and the aim is to find out if there is a positive effect in the groups. Here the findings are hypothesis generating and the results require confirmation in future trials; (2) supportive analysis where positive impact has been shown, and the further analysis wants to establish consistency of these findings among the various subgroups; (3) inferential analysis where the aim is to determine treatment efficacy in a predefined targeted subgroup (Alosh et al. 2017).

1.3.2 Indications for subgroup analysis

Subgroup analysis could be could be used to explore the effect two potential treatment heterogeneity - either effect related to risk or effect related to pathophysiology (Rothwell 2005). It may also be due to reasons of essential clinical questions related to the practical application of treatment or under-utilisation of treatment in routine clinical practice due to uncertainty about the benefit.

Several motivations have been reported to drive these indications such as the need to evaluate the robustness of the overall result across subgroups and evaluation of the risk-benefit profile of treatment on the different subgroups. Others are the requirement of explaining the variation in treatment effects, because pulling results from a heterogeneous population can increase the risk of missing significant effects. Also, the observed general effects may not be precise for individual patients. It can also aid in drug labelling.

1.3.3 Method and guideline in conducting subgroup analysis

In subgroup analysis, study samples are broken down into a subset of participants based on shared characteristics, with the goal of exploring the differences in how people respond to the intervention. In doing this, variables should be limited to baseline characteristics to ensure that they were not affected by the study treatment. To avoid ambiguity, the objectives must be defined upfront from the onset and the reasons for the subgroup explained scientifically based on sound hypothesis and reporting of findings should include all the subgroups and not a selected few. Statistical methods for conducting exploratory subgroup analysis include use of marginal structural modelling and propensity matching.

Due to the crucial role well-conducted subgroup analysis could play in trials, many regulatory bodies encourage their use by researchers to investigate the consistency of treatment effects

and the impact of such findings on the interpretation of clinical trials (Group 1999; Alosh et al. 2015; Wang and Hung 2014; Maggioni et al. 2007). However, subgroup analysis remains a controversial issue with many protagonists and antagonists drawn between clinicians and statisticians, a situation that has previously been referred to as the “clinicostatistical” tragedy (Feinstein 1998). There is every need to ensure adherence to laid down guidelines in undertaking and reporting subgroup analysis in order to avoid the pitfalls.

Subgroup analysis can aid the design of future trials; therefore there is a need to reinforce the foundation on which researches are built through ensuring uniform reporting (Wang et al. 2007). In a bid to encourage a more explicit and more complete reporting of all aspects of RCT, including subgroup analysis, the CONSORT guidelines were proposed in 1996 and subsequently edited in 2001 (Altman et al. 2001). Despite these efforts, review of several publications show that most researchers do not obey these rules. These flagrant downplaying of the set guidelines are the reasons while many commentators oppose the use of subgroup analysis while others refer to them as attempts at data mining.

Planned subgroup analysis should be documented in the trial registry at the stage of protocol development and ensure adherence to the guidelines for protocols of RCTs, such as the Standard Protocol Items Recommendations for Interventional Trials [SPIRIT] (Chan et al. 2013). It has also been canvassed that journals request access to a protocol of statistical analysis plans for reviews.

The robustness of subgroup analysis can be significantly enhanced by considering multiple factors rather than individual baseline characteristics. Risk of disease outcome calculated from prespecified externally validated formula can be used to categorise them into separate groups by incorporating several baseline characteristics.

Results of subgroup analysis should be exploratory because significant testing in it is inappropriate unless alpha levels needed to achieve significance is attributed to a comparison of interest in advance. Forest plot with the level of baseline factors is the most appropriate way of presenting information about plausible treatment effects (Cuzick 2005; Wactawski-Wende et al. 2006). The confidence interval in such a plot should not be used to indirectly assess statistical significance based on whether they exclude a null effect; doing so is the same as using subgroup analysis to look for significant testing (Hayward et al. 2006; loannidis and Lau 1998).

If the effect of intervention varies in the subgroup, this is referred to as effect modification of the intervention on the outcome due to the additional presence of subgroup variables. Tests of interactions like multivariable modelling are used to test the significance of these differences. The credibility of subgroup analysis is improved if confined to the primary outcome and a few predefined subgroups based on biologically plausible hypothesis including factors used to stratify randomisation (Assmann et al. 2000).

1.3.4 Limitations to using subgroup analysis and ways to avoid them

Patients in a trial have multiple characteristics simultaneously. However, in subgroup analyses, these characteristics are erroneously considered one at a time. One glaring consequence of this is multiple testing which could lead to type 2 error (false negative result). Also, in doing several subgroup analyses, there is the problem of reduced sample size and loss of statistical power to detect any effect. Embarking on post hoc analysis after inspection of data most likely leads to error, and this has led to the conclusion held by some that reporting of subgroup analysis is characterised by poor practice (Parker and Naylor 2000; Pocock, Hughes, and Lee 1987; Pocock et al. 2002; Yusuf et al. 1991).

Suggestions have been made on ways to avoid the dangers in subgroup analysis, and this begins at the stage of planning before randomisation (Cook, Gebski, and Keech 2004). The subgroups need to be defined a priori, stating reasons for selection. The appropriate test for hypothesis should be employed, interaction used to test for heterogeneity, and adequate adjustment should be made for multiple testing.

In interpreting the result, the general trial findings should be explained, rather than the subgroup, since it has less power to detect a therapeutic effect, the discussion should be done considering biological knowledge and findings from an independent study.

In evaluating the results of a subgroup analysis attention should be paid to the chance of association, biological gradient, consistency of findings with previous works, the presence of confounders and the plausibility/coherence of report.

The validity of subgroup analysis results can be evaluated through some criteria: Is the noticed difference suggested by comparison within or between the group, what time was the hypothesis generated? Before data inspection (a priori) or after (post hoc); how large is the magnitude of the effect and if it was statistically significant. Also, the other results should confirm the same findings seen reported by the indirect evidence to support the subgroup effect (Oxman and Guyatt 1992).

1.4 Overview of tuberculous pericarditis with relevance to the IMPI trials

1.4.1 Introduction

Tuberculosis (TB) is a prominent health concern globally and a leading cause of mortality and morbidity in low- and medium-income countries [LMICs] (WHO 2013). It is now the world's leading cause of death from infectious diseases, exceeding acquired immune deficiency

syndrome (HIV/AIDS) and malaria. The World Health Organization (WHO) 2018 report estimates about 10.4 million new cases of and tuberculosis worldwide, and 1.674 million deaths yearly (1.3 million HIV negative and 374,000 HIV positive) from the disease, with approximately 95% of these patents residing in LMICs (WHO 2017).

Tuberculous pericarditis is a disease caused by infection/inflammation of the pericardial covering of the heart by *Mycobacterium* tuberculosis. Pericarditis is the most common disease of the pericardium in clinical practice and refers to the inflammation of the heart covering; it is responsible for 0.1-0.2% of all hospital admissions (Kyto, Sipila, and Rautava 2014; Lange and Hillis 2004) and the cause of about 5% of emergency room presentations for chest pain without myocardial infarction. The aetiology of pericarditis is based on the local epidemiology, in Europe, the majority of cases are idiopathic (mainly viral) or from malignancies, with tuberculosis accounting for about 4% (Imazio, Brucato, et al. 2010). However, in Africa and India, tuberculosis is responsible for 70-80% (in HIV negative) and up to 90% (in HIV positive) cases of pericarditis (Adler, Charron, Imazio, Badano, Barón-Esquivias, Bogaert, Brucato, Gueret, Klingel, Lionis, et al. 2015; Imazio, Brucato, et al. 2010). This report makes tuberculosis the most prominent cause of pericarditis in Africa and other parts of the world with a high TB burden.

According to WHO report, the high morbidity and mortality from TB is mostly contributed to by the difficulty in diagnosis and delayed initiation of treatment in tuberculous pericarditis and other forms of extrapulmonary TB (Mayosi et al. 2008a; Larrieu et al.). The reason for this is the paucibacillary nature of extrapulmonary TB leading to the low yield of *Mycobacterium* TB required for culture, which is the gold standard for the confirmation of the diagnosis of TB. The delayed diagnosis results in a long time before the commencement of treatment, which may affect the outcome.

1.4.2 Epidemiology

The incidence of pericardial involvement following pulmonary TB is estimated to be 1-8% (Lorrel 1997; Denk et al. 2016). Autopsy studies done before the HIV/AIDS era show that there is pericardial involvement in up to 1-2% of patients known to have had pulmonary TB (Fowler 1991; Trautner and Darouiche 2001).

The epidemic of HIV/AIDS has led to an increase in the morbidity and mortality of TB and consequently of TBP; this can be attributed to the fact that the 10% lifetime risk of TB in an immunocompetent adult exponentially increases to 10% per year and, in cases of severe immunodeficiency, it is estimated to be 30% per year. During the pre-antibiotics era diagnosis of tuberculosis led to certain death with a reported mortality of 80-90%. However, the introduction of anti-tuberculous drugs led to a reduction in case fatality to 8-17%, but with the scourge of HIV/AIDS has resulted in a significant pushback in the success achieved, with a reported mortality of 17% in HIV negative patients and 40% in HIV positive patients in an African multinational study (Mayosi et al. 2008a).

Tuberculous pericarditis (TBP) contributes to the increased mortality of tuberculosis and is the most frequent cause of constrictive pericarditis in Africa and Asia (Mayosi, Wiysonge, Ntsekhe, Volmink, Gumedze, Maartens, Aje, Thomas, Thomas, Awotedu, et al. 2006). It is responsible for 50%-70% of pericardial disease, and 7% of cases of heart failure in Africa (Mayosi, Wiysonge, Ntsekhe, Volmink, Gumedze, Maartens, Aje, Thomas, Thomas, Awotedu, et al. 2006). The incidence of TBP in Sub Saharan Africa is increasing because of HIV epidemics, as it is leading the resurgence of TB. Large pericardial effusion occurring in up to 90% of HIV infected patients living in Tuberculous endemic areas are caused by tuberculosis (Reuter, Burgess, and Doubell 2005; Cegielski et al. 1994; Maher and Harries 1997). In the Sub-Saharan Africa Survey of Heart Failure (THESUS–HF), conducted in 9 African countries between 2007-2010, pericardial effusion with tamponade was the cause of acute heart failure

in 6.8% of the patients (Damasceno et al. 2012). Approximately 65.6% of the cohorts in the first investigation of the management of pericarditis (IMPI-1) trial drawn from South Africa, Malawi, Mozambique, Kenya, Nigeria, Sierra Leon, Uganda, Zimbabwe were HIV positive (Mayosi et al. 2014). In a study from Malawi more than 60% of patients with pericardial TB were HIV positive (Maher and Harries 1997). Tuberculosis is responsible for 37% of patients with large effusion in Kuwait (Uthaman et al. 1997), while in the United Kingdom the immigrant communities account for 26% of pericardial effusion (Gibbs et al. 2000).

1.4.3 Pathogenesis

The occurrence of pericarditis follows inoculation of the bacteria into the pericardial space, resulting pathologically in polymorphonuclear leucocytosis (Figure 1.1) with abundant bacilli and granular formation (Spodick 1956). The bacilli gain access to the pericardium either by retrograde lymphatic spread from the mediastinum, paratracheal or parabronchial lymph nodes, through the hematogenous spread (common in immunosuppression). Direct contiguous spread from adjacent structures such as lungs, pleura and spine could be another rare route (Spodick 1956). The pathological changes seen in TBP are because of the body's immune response to *Mycobacterium* TB as it penetrates the pericardium, and this stimulates lymphocyte to release lymphokines which activate macrophages leading to granuloma formation. TH-1 lymphocytes have been shown to engineer the hypersensitivity reactions that lead to the development of effusion as demonstrated by the elaboration of the cytokine profile (Burgess et al. 2002). Also anti-myolemma antibodies mediated cytokines aid the exudation of fluid in TBP as shown by complement-fixing anti-myolemma and anti-myosin type antibodies seen in patients with tuberculous pericardial effusion (Maisch, Maisch, and Kochsiek 1982). In the literature, there are four pathological phases of tuberculous pericarditis and the clinical pictures seen in practice follow these phases (Table 1.2).

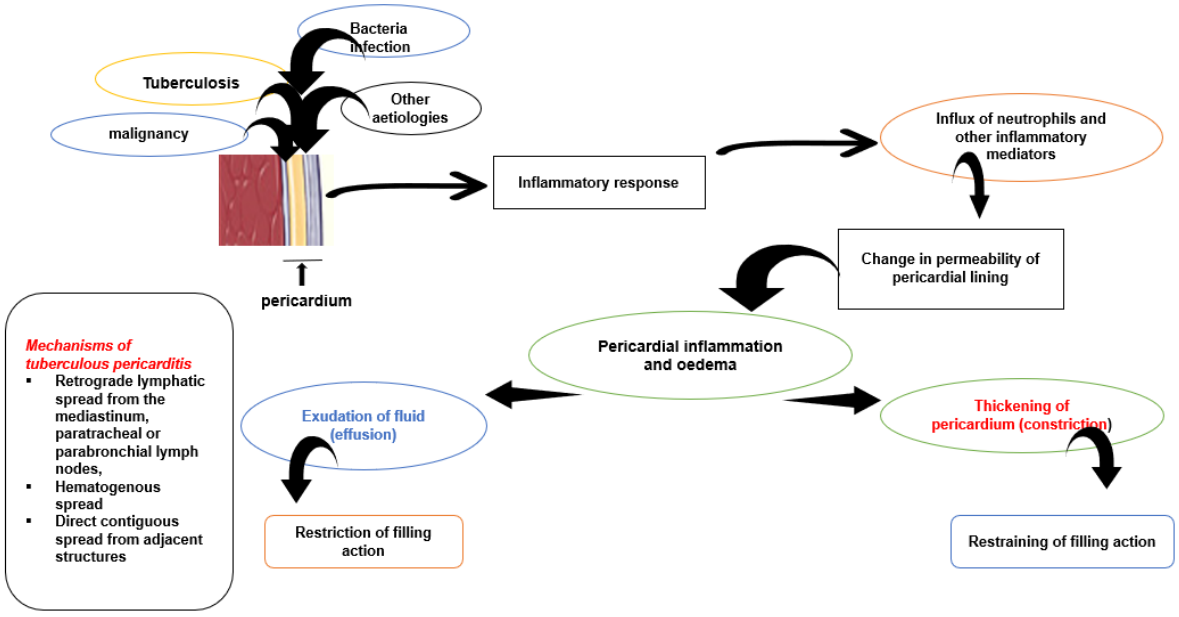


Figure 1.1: Pathophysiological changes in pericarditis

Table1.1: Stages of Tuberculous pericarditis (Ntsekhe and Mayosi 2013a)

Stage 1	
• Pathological bases	Fibrinous exudation predominates, occurrence of polymorphonuclear leucocytosis is first seen with relatively abundant mycobacteria. There is loose organization of macrophages and T cells with early granuloma formation (HIV patients with low CD4 T cells with fewer granuloma due to low immune response).
• Pathological manifestations	Dry stage (the least common form seen).
• Clinical manifestation	Patients present in acute pericarditis with chest pain, pericardial friction rub and widespread ST elevation without effusion.
Stage 2	
• Pathological bases	There are predominantly lymphocytic exudates with monocytes and foam cells; Presence of serosanguineous effusion is seen.
• Pathological manifestation	Effusive stage (most common form seen)
• Clinical manifestation	(1) Patients present with features of heart failure and /or cardiac tamponade due to moderate to large pericardial effusion. (2) Effusive constrictive pericarditis with coexistence of visceral constrictive pericarditis and simultaneous compressive pericardial fluid. The former become obvious following pericardial drainage.
Stage 3	
• Pathological bases	At this stage there is absorption of effusion, granulomatous caseation becomes organized and pericardial thickening occurs due to fibrin, deposition of collagen and ultimately fibrosis.
• Pathological manifestation	Adsorptive stage
• Clinical manifestation	Symptoms and signs compatible with constrictive pericarditis but radiological and echocardiographic evidence of thick fibrinous fluid around the heart.
Stage 4	
• Pathological bases	Constrictive scarring (the fibrosing visceral and parietal pericardium contracts on the cardiac chambers). Calcification leads to encasing of the heart in a fibrocalcific skin. Diastolic filling is impeded, causing the classic syndrome of constrictive pericarditis.
• Pathological manifestation	Constrictive stage
• Clinical manifestation	Constrictive pericarditis symptoms and signs predominate; and echocardiography confirms the diagnosis with no residual fluid in the pericardium.

(Adapted with permission from Springer Nature Science. Ntsekhe M, Mayosi BM. Tuberculous pericarditis with and without HIV. Heart Failure Reviews. 2013;18(3):367-73)

1.4.4 Clinical Presentation

Clinical presentation depends on the stage of the disease; however, some patients can be asymptomatic and the diagnosis of TBP made incidentally following presentation for other reasons. The Tygerberg score (Table 1.3) was developed to aid accurate and prompt diagnosis of tuberculous pericarditis in resource-limited settings where TBP is endemic (Reuter, Burgess, et al. 2006a). A total of 6 and above has a sensitivity of 86% and a specificity of 85% in reaching a diagnosis of TB pericarditis (Reuter et al. 2007).

Table 1.2: Tygerberg score

Clinical Parameter	No of Point.
1. Weight loss	1
2. Night Sweats	1
3. Fever	2
4. Serum globulin >40 g/l	3
5. Blood leukocyte count $<10 \times 10^9$/l	3
Total	
A total score of 6 or more is highly suggestive that tuberculosis is the cause of the pericarditis.	

About 3 - 8% of patients with TBP can present as acute pericarditis (Mayosi, Wiysonge, Ntsekhe, Volmink, Gumedze, Maartens, Aje, Thomas, Thomas, and Awotedu 2006; Mayosi et al. 2014), with complaint of pleuritic chest pain, finding of pericardial friction rub, electrocardiographic ST-T wave changes and PR depression, with or without new/worsening pericardial effusion [at least two of these can be used to make the diagnosis] (Klein et al. 2013; Imazio et al. 2014; Imazio 2012). Other signs and symptoms could include evidence of systematic inflammation, fever and raised markers of acute infection such as white cell count, ESR and C-reactive proteins. This condition has been attributed to the inoculation of tubercle bacilli into the pericardium, said to be characterised pathologically by polymorphonuclear leucocytosis with abundant bacilli and granuloma formation (Fowler 1991; Spodick 1956). The diagnosis is suggested in TB endemic areas by finding of constitutional symptoms, lack of

response to conventional antibiotics and resolution of symptoms following anti-tuberculosis medications (Mayosi, Burgess, and Doubell 2005).

Two broad mechanisms drive the other clinical presentation of pericarditis; fluid accumulation around the heart, referred to as effusion, which may lead to the restraining of contraction of the heart (tamponade) or thickening of the pericardium without effusion which results in restriction of the pumping action of the heart (constriction) [Figure1.1 &1.2]. These two scenarios can usually present in three clinical forms: pericardial effusion, and its complications, constrictive pericarditis or a combination of effusion and constriction (effusive-constrictive pericarditis). Despite the discussion of these as separate clinical entities, there is much overlap in their manifestations (Mayosi, Wiysonge, Ntsekhe, Volmink, Gumedze, Maartens, Aje, Thomas, Thomas, Awotedu, et al. 2006; Syed and Mayosi 2007).

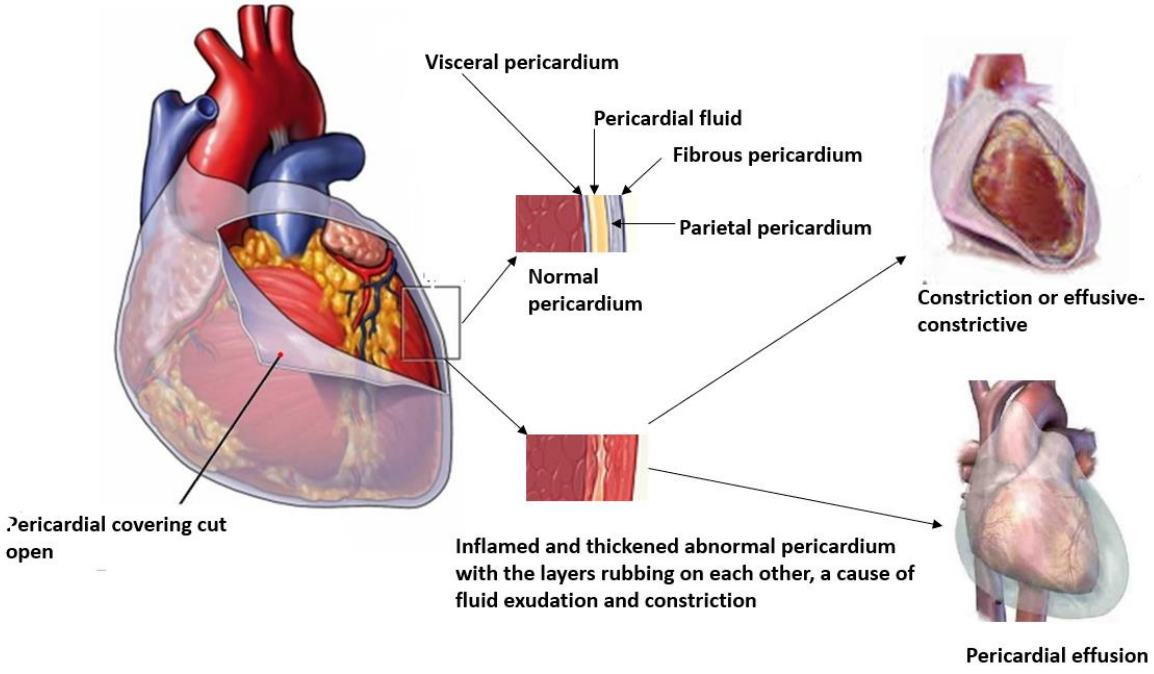


Figure 1.2: Natural history of Pericarditis

1.4.4.1 Pericardial Effusion

The pericardial sac usually contains 10-50 ml of plasma ultrafiltrate that lubricates the pericardial layers; the body homeostasis ensures that this quantity of fluid remains constant. However, alteration of this standard regulatory mechanism can lead to an increase in pericardial fluid. This can be due to reduced absorption (transudate), as seen in the situation of increased systemic venous pressure like the congestive cardiac failure or pulmonary hypertension or from inflammation (exudate) as in *Mycobacterium* tuberculosis, bacterial infection or neoplasm. Development of pericardial effusion can be insidious depending on such factors as rapidity of accumulation of fluid, pressure-volume balance and the underlying cardiac pathology status (Spodick 2003); symptoms are also non-specific and can include fever, night sweats, fatigue and weight loss (Hageman, D'Esopo, and Glenn 1964).

If fluid accumulation is rapid as is seen in trauma or during cardiac interventions, small acute pericardial effusions can lead to the dramatic development of tamponade physiology; with increased diastolic filling pressure, resulting in systemic and pulmonary congestion, leading to tachycardia, hypotension typical of cardiac tamponade (Spodick 1997). However, hemodynamically, slowly accumulating moderate-sized or even large pericardial effusions can be well tolerated. In this situation, pericardial effusion presentation is usually subacute or chronic if fluid collection is slow and in cases with adequate cardiac compensatory mechanisms, large pericardial fluid may be asymptomatic and findings incidental (Ivens, Munt, and Moss 2007). Therefore, the signs and symptoms of pericardial effusion are determined by the rate of accumulation of fluid, magnitude of pericardial fluid induced compression, compliance of the visceral pericardium and degree of inflammation (Ntsekhe and Mayosi 2013b; Shabetai 1976).

Physical presentations include chest discomfort, tachypnoea, dyspnoea on exertion, progressing to orthopnoea. Occasionally there could be a cough with dysphagia (Roy et al. 2007). Most patients become weak and anorectic with fainting and syncope (Roy et al. 2007).

Cardiac tamponade, a life-threatening slow or rapid compression of the heart due to the pericardial accumulation of fluid, can be a grave complication of pericardial effusion (Imazio, Mayosi, et al. 2010; Ristić et al. 2014; Roy et al. 2007). The clinical signs seen include the following: tachycardia, pulsus paradoxus (defined as an inspiratory decrease in systolic arterial pressure of 10mmHg during normal breathing), raised jugular venous pressure (JVP), low blood pressure (hypotension), muffled heart sounds, reduction in electrocardiographic voltage with electrical alternans and an enlarged cardiac silhouette on chest X-ray with slow-accumulating effusions (Figure 1.5A & 1.6A). Pulsus paradoxus is a crucial finding in cardiac tamponade. The exaggerated ventricular interdependence occurring in cardiac tamponade when the overall volume of cardiac chambers becomes fixed is the reason for pulsus paradoxus. Changes in the volume of one side of the heart lead to changes on the other side (Adler, Charron, Imazio, Badano, Barón-Esquivias, Bogaert, Brucato, Gueret, Klingel, Lionis, et al. 2015)

1.4.4.2 Constrictive pericarditis

Though tuberculosis has become a rare cause of constrictive pericarditis in developed countries, it remains a significant cause in developing countries and most regions with high TB burden (Mutyaba et al. 2014) Other causes include purulent pericarditis from a bacterial cause, neoplasm, while it is rare in viral pericarditis. Factors such as duration of constriction, its severity and presence of ongoing pericardial inflammation can all influence the clinical presentation of constrictive pericarditis (Spodick 1997).

Clinical signs of congestion will include engorgement of neck veins; peripheral oedema is uncommon. Liver enlargement leading to abdominal swelling and discomfort are typically more consistent with constriction rather than effusion (Strang, Kakaza, et al. 1988; Reuter et al. 2007). Pulmonary oedema results in a cough and dyspnoea, while pleural effusion can be seen (Hageman, D'Esopo, and Glenn 1964).

1.4.4.3 Effusive-constrictive pericarditis

Effusive-constrictive pericarditis refers to coexistent of features of pericardial effusion and constriction, with the signs of the later developing after fluid accumulation is removed (Ntsekhe et al. 2013a). It is said to result from thickened non-compliant visceral pericardium secondary to chronic inflammation (Hancock 1971; Russell et al. 2008). This finding occurs in up to 50% of tuberculous pericarditis and some reports have attributed it to a more severe outcome (Ntsekhe et al. 2012). Both clinical features of pericardial effusion and constrictive pericarditis can exist individually or both at the same time (Figure 1.7). During pericardiocentesis for a patient initially considered to have uncomplicated cardiac tamponade, the diagnosis often becomes apparent when clinical signs persist after removal of the fluid (Sagristà-Sauleda et al. 2004). Monitoring of right heart pressure, systolic arterial blood pressure and intra-pericardial pressures are recommended whenever possible during elective pericardiocentesis. This is because, in some cases, pericardiocentesis can result in severe tricuspid regurgitation and right heart failure with persistently elevated right atrial pressure (Kuroda et al. 2016; Anguera, Paré, and Perez-Villa 1997; Klimis et al. 2018). Non-invasive imaging modalities may equally be used to reach a diagnosis of effusive-constrictive (Ntsekhe et al. 2012). The epicardial layer of the pericardium, which is responsible for the constrictive component of this process, is not typically thickened to the degree that is detectable in imaging studies.

Following pericardiocentesis for cardiac tamponade, effusive-constriction can be diagnosed by careful detection of Doppler features of constriction; it can also be suspected in these cases without hemodynamic monitoring. Cardiac magnetic resonance imaging can be used in establishing the diagnosis of constrictive pericardial disease. Through it, the pericardial thickness can be evaluated, as well as cardiac morphology, and function. It can also be used to study the intrathoracic cavity structures and help in differentiating constrictive pericarditis from restrictive cardiomyopathy (Cosyns et al. 2014). In effusive-constrictive pericarditis,

definitive treatment is by visceral pericardiectomy because the visceral pericardial layer, rather than the parietal layer, is the cause of the heart constriction in this case (Cosyns et al. 2014; Strang 1984). However, this delicate surgery should be reserved for performance at hospitals with requisite experience in pericardiectomy for pericarditis as it is technically difficult requiring sharp dissection of many small fragments until an improvement in ventricular motion is observed (Adler, Charron, Imazio, Badano, Barón-Esquivias, Bogaert, Brucato, Gueret, Klingel, Lionis, et al. 2015).

1.4.5 Diagnosing Tuberculous pericarditis

1.4.5.1 Confirmation of the presence of pericardial disease

The chest x-ray shows enlarged cardiac shadows (Figure 1) with up to 90% of those with constriction having a cardiac-thoracic ratio higher than 55%, and calcification noticed in less than 5% (Strang 1984). Up to 30% of patients may have features of active pulmonary tuberculosis, and another 50% with accompanying pleural effusion noticed on chest x-ray (Rooney, Crocco, and Lyons 1970). In electrocardiography, the presence of microwaves (Figure 1.5B) with a QRS amplitude less than 5mm in the limb leads and less than 10mm in the chest leads are obvious findings.

Echocardiography is an essential non-invasive tool in making a diagnosis of TBP. The properties of being sensitive, specific, non-invasive and readily available at bedside, make M-mode and 2-dimensional Doppler echocardiography the gold standard and most effective technique for the diagnosis of pericardial effusion (Horowitz et al. 1974). Pericardial effusion appears as echo-free space surrounding the heart medial to the position of descending aorta in 2D echocardiography, often noticed to be swinging in cases of tamponade (Figure 1.5C &1.6D). A small collection of 25-50ml of pericardial fluid can be physiologic and may be visible. The size of the echo-free space has been used to grade the severity of pericardial effusion and is often used in determining the feasibility of percutaneous drainage; small effusion is less

than 1cm, moderate 1-2cm and large more than 2cm. Fibrinous strands in visceral pericardium are typical but not specific of TBP (Liu et al. 2001; Ku et al. 2003; Mayosi 2009).

In pericardial tamponade, echocardiographic features include swinging heart, right ventricular/right atrial diastolic collapse as seen on the 2D image, increased respiratory variation of E wave velocity across mitral valve (Figure 1.5D) more than 25% (Ha et al. 2002). The inferior vena cava (IVC) plethora with less than 50% collapse noticed in the presence of tamponade or severe constriction (Ha et al. 2002).

In situations of a technically limited echocardiographic study, computed tomography (CT) or magnetic resonance imaging (MRI), may be used to identify the characteristics of pericardial effusion and tamponade (Maisch et al. 2004; Sagrista-Sauleda, Merce, and Soler-Soler 2011; Verhaert et al. 2010). MRI and CT scan (Figure 1.7) where available can give additional information, such as the degree of inflammation and accurate measurement of pericardial thickness (Yared et al. 2010; Feng et al. 2011). Given the central positive position of echocardiography in making a diagnosis and the safety concerns in acutely ill patients, the clinical utility of CT and MRI is questionable. However, they play adjunctive roles to echocardiography, especially in situations that show atypical hemodynamic states, where the presence and severity of tamponade are doubtful, or when there are other unexplained conditions (Verhaert et al. 2010).

1.4.5.2 Confirmation of aetiology of tuberculosis

Establishing tuberculosis as the aetiology of pericarditis may be difficult due to the paucibacillary nature of TBP and low diagnostic yield. The gold standard investigative modality for TB is a culture of tissue and fluid (Reuter, Burgess, et al. 2006b; Heller et al. 2010). However, this often takes time and is not readily available for use in most of the populations with a high TB burden, leading invariably to a delay in the commencement of treatment, ultimately affecting patient management and eventual outcome.

Diagnosis can be categorised as follows: 1) Definite TBP: Diagnosis confirmed on a pericardial sample made by finding positive acid and alcohol fast bacilli on microscopy, a positive microbiological culture of *Mycobacterium tuberculosis*, the presence of caseating granulomata in histology or positive mycobacterial DNA detected by PCR in tissue or fluid (Mayosi et al. 2014). 2) Probable TBP: Presence of a lymphocyte predominant pericardial exudate with increased ADA> 4OIU/L, positive polymerase chain reaction, positive isolation of *Mycobacterium* TB from other sites 3) Non-TBP where there is an alternate diagnosis for the cause of pericarditis.

To prevent the challenge of early diagnosis, the World Health Organization and other research bodies have, in recent years, invested heavily in finding prompt and cost-saving diagnostic tools. The emphasis has been on the development of point-of-care highly sensitive and specific diagnostic methods that can detect *Mycobacterium* TB in EPTB (Nema 2012). Currently, available modalities include adenine deaminase assay (ADA), polymerase chain reaction (PCR) based gene Xpert MTB/RIF, with a sensitivity of 25-96.6% (Lawn et al. 2013). These were initially developed for pulmonary TB, but now in use in other EPTB like TBP. However, lower sensitivity has been shown in pleural and pericardial fluids (Friedrich, von Groote-Bidlingmaier, and Diacon 2011). Also, they exhibit lower sensitivity in smear-negative compared to positive smear patients (Vadwai et al. 2011). Cost of these investigations is also a significant challenge in limited resource settings (Table 1.2).

Interferon-gamma has been demonstrated in TB pericarditis compared to non-TB pericarditis with a cut-off of 50ng/ml resulting in 97% sensitivity, 100% specificity and diagnostic accuracy of 95% (Reuter, Burgess, et al. 2006b). The diagnostic efficiency is unrelated to HIV infection. Interferon-gamma release assays such as QuantiFERON-TB gold are currently in use in TB diagnosis in most developed countries. It has a pooled sensitivity of 75% among patients with active TB (Pai and Menzies 2007) and high specificity of 94%

when tested against patients with non-TB *Mycobacterium* (Dewan, Grinsdale, and Kawamura 2007).

1.4.6 Promoting Prompt Diagnostic Modalities for Tuberculous pericarditis

The year 2015 marked the millennium development goals (MDG) and global TB target deadline of reduction of TB disease burden. Post-2015 WHO target is shifting to sustainable development goals (SDG) of ending TB as a public health problem (2016-2030). This it plans to achieve by, among other things, the pursuance of strengthening of diagnostic and laboratory testing to achieve the stated objectives. WHO, in this renewed mandate, advocate for the early diagnosis of TB and universal drug susceptibility testing (DST). They also highlight the critical role of laboratories in the post-2015 era for rapidly and accurately detecting TB and drug resistance (Uplekar et al. 2015).

In keeping with this, WHO and different research bodies have been evaluating other modalities with the aim of ensuring early, prompt and cost-saving diagnosis. To achieve this, they are encouraging research at the development of point of care highly sensitive and specific diagnostic methods that can identify active *Mycobacterium* TB (Nema 2012).

In 2016 the World Health Organization (WHO), reviewed and recommended four new diagnostic tests (one for TB) and (three for multi-drug resistant TB [MDR-TB]). A next-generation cartridge called Xpert Ultra, and a new diagnostic platform called GeneXpert Omni is in development. The WHO assessed some of these emerging diagnostic modalities in 2017 (Organization 2016) and the 2018 global tuberculosis report (Organization 2018), listing them as TB diagnostics under development (Table 1.3).

Table 1.3: Diagnosis of Tuberculous Pericarditis

Modalities currently in use in most LMICs	Strengths	Limitations
IMAGING		
Chest x-ray	Enlarged cardiac shadows in up to 90%, calcification seen in about 3%. Pulmonary TB seen in 30%	Majority may not have pulmonary TB In presence of HIV/AIDS, features may be non-specific with false negative reports.
2D Echocardiography	Gold standard for making diagnosis of large effusion, and able to spot and aid in management of tamponade	Requires expertise and may not be commonly available in rural settings
CT Scan & MRI	Gives additional information on degree of inflammation, pericardial thickening and characteristics of effusion	Cost implications, safety concerns in severely ill patients due to enclosed space.
DIRECT LABORATORY METHODS		
Microscopy	The first line screening modality, cheap and commonly available in remote areas	Low sensitivity in paucibacillary conditions like TBP. Smear negative conundrum.
Culture	Gold standard in establishing diagnosis	A challenge in paucibacillary TB, may need tissue biopsy to strengthen yield, takes 6-8 weeks for result to be available leading to delayed treatment
INDIRECT		
ADA	Highly sensitive at ≥40IU/L	Yield may be reduced in paucibacillary TB
PCR based like Xpert MTB/RIF	Sensitivity of 25-90% Of great value in MTB	Lower sensitivity in pleural and pericardial fluid and smear negative

Modalities in use in HICs	Strengths	Limitations
Interferon gamma release assays (IGRAs) Example QUANTEFERON gamma, unstimulated interferon assays	Aids prompt diagnosis. 90% sensitive and 100% specific.	Not suited for LMICs because of inability to differentiate latent from active infections
Nucleic acid amplification test	Quick diagnosis	High cost
High performance liquid chromatography		
Radiometric and non-radiometric detection in liquid culture		
Antibody susceptibility testing		
Line probe and LAMP assays		
Newer innovations		
MTB/RIF ultra assays	An improvement on MTB Gene Xpert with increased sensitivity Useful in difficult-to-diagnose and vulnerable populations, such as children and people living with HIV, and in those with extra-pulmonary TB. Superior to liquid culture	Detects both viable and non viable bacilli. .
MicraRNA assays	miRNA is expressed differently between active and latent TB, an attribute that has opened a potentially fascinating portal for early and prompt diagnosis of TB	Still at developmental stage
Urinary Lipoarabinomannan	Very useful in severe immunosuppression and removes the need for biological samples from disease site.	Only useful in severe illness. Cannot differentiate latent and active disease. Limited in paucibacillary TB

1.4.6.1 Xpert MTB/RIF

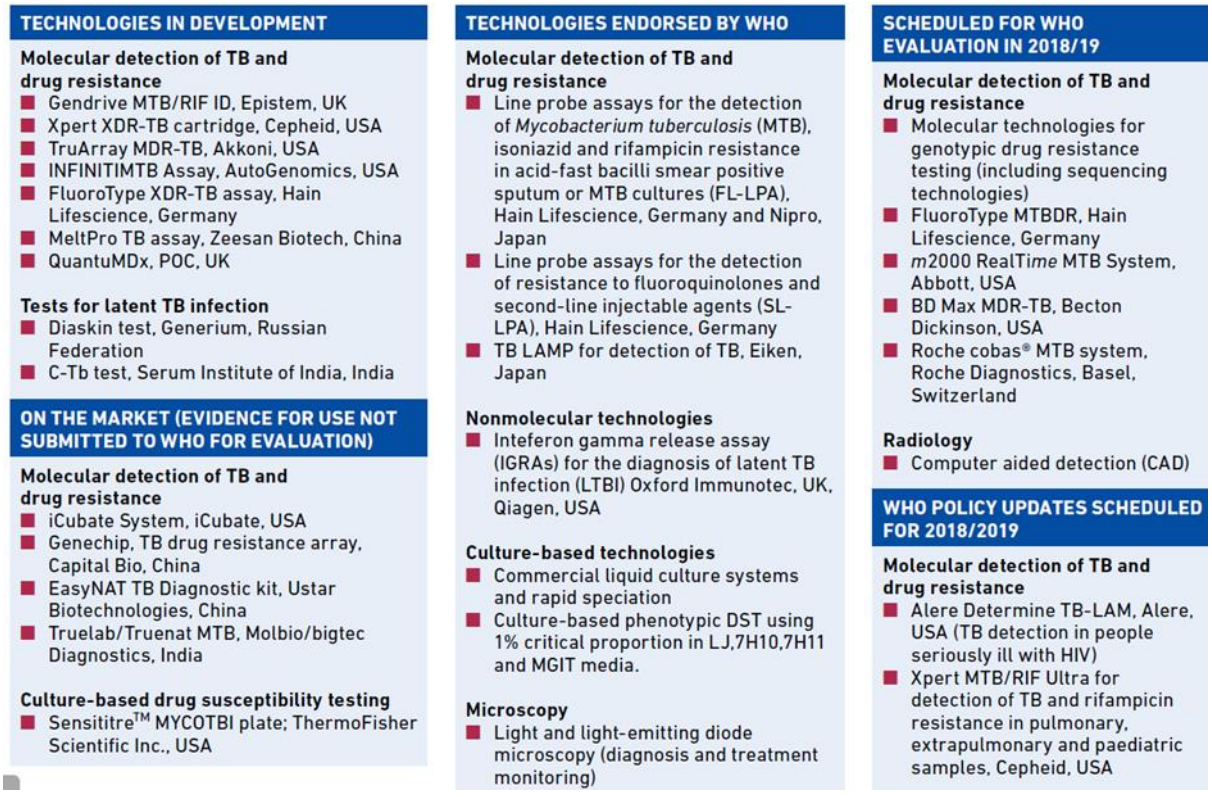
One landmark event in TB research was the development in 2010 of Xpert MTB/RIF automated molecular assay (Cepheid CA the USA) for rapid TB diagnosis and rifampicin resistant detection of markers of MDR-TB (Purohit and Mustafa 2015). The laboratory technique was developed and endorsed specifically for detection of pulmonary TB using sputum. Its use has however recently been extended to EPTB and; in all but one study, the sensitivity ranged from 25%-96.6% (Lawn et al. 2013). However, lower sensitivity has been documented in CSF, pleural and pericardial fluids,(Friedrich, von Groote-Bidlingmaier, and Diacon 2011). Also, cost is a limitation as well as lower sensitivity in smear-negative compared to smear-positive (Vadwai et al. 2011). In an IMPI-1 diagnostic substudy on patients with TBP, Xpert MTB/RIF was shown to have a lower sensitivity and negative value compared to

unstimulated interferon gamma and adenine dinucleotide (Pandie et al. 2014). Also, in a Cochrane systematic review looking at the use of Xpert MTB/RIF in EPTB, eighteen studies with median sample size (IQR) of 13 (3-19) specimen were identified that evaluated pericardial fluid. Results of the review reported a TB prevalence of 20% with sensitivity and specificity of 25-100% and 69-100% respectively. Reporting on seven studies (324 specimens), the pooled sensitivity and specificity at 95% confidence interval for Xpert in this review was 65.7 [46.3-81.4) and 96.0% (85.8-99.3] (Kohli et al. 2018).

1.4.6.2 Unstimulated Interferon assay

Use of interferon gamma (IFNγ) to diagnose TB pericarditis has been demonstrated at a cut-off of 50pg/ml, with 92% sensitivity, 100% specificity and 95% diagnostic accuracy (Reuter, Burgess, et al. 2006b). This diagnostic efficacy is unrelated to HIV infection. The principle has led to the development of a highly sensitive and accurate enzyme-linked immunospot (ELISPOT) test that detects IFNγ producing T cells specific for *Mycobacterium tuberculosis* antigen (Ewer et al. 2003; Liebeschuetz et al. 2004). Currently, IFNγ related analysis (IGRA's), such as QUANTIFERON TB gold, are in use in TB diagnosis in most developed countries, with a pooled sensitivity of 75% among patients with active TB (Pai and Menzies 2007) and high specificity of 94% when tested against patients with non-TB *Mycobacterium* infection (Dewan, Grinsdale, and Kawamura 2007). However, WHO did not recommend it for use in diagnosis in LMICs because of its inability to differentiate active from latent infection (WHO 2011). Also, very few studies have evaluated their use in pericardial and other extra-pulmonary TB, and there is also the concern over inconclusive results in immune-compromised due to anergy (Vincenti et al. 2007).

Table 1.4: Progress in the development of TB diagnostics (August 2018) [a]



TECHNOLOGIES IN DEVELOPMENT

Molecular detection of TB and drug resistance
- Gendrive MTB/RIF ID, Epistem, UK
- Xpert XDR-TB cartridge, Cepheid, USA
- TruArray MDR-TB, Akkoni, USA
- INFINITIMTB Assay, AutoGenomics, USA
- FluoroType XDR-TB assay, Hain Lifescience, Germany
- MeltPro TB assay, Zeesan Biotech, China
- QuantuMDx, POC, UK

Tests for latent TB infection
- Diaskin test, Generium, Russian Federation
- C-Tb test, Serum Institute of India, India

ON THE MARKET (EVIDENCE FOR USE NOT SUBMITTED TO WHO FOR EVALUATION)

Molecular detection of TB and drug resistance
- iCubate System, iCubate, USA
- Genechip, TB drug resistance array, Capital Bio, China
- EasyNAT TB Diagnostic kit, Ustar Biotechnologies, China
- Truelab/Truenat MTB, Molbio/bigtec Diagnostics, India

Culture-based drug susceptibility testing
- Sensititre™ MYCOTBI plate; ThermoFisher Scientific Inc., USA

TECHNOLOGIES ENDORSED BY WHO

Molecular detection of TB and drug resistance
- Line probe assays for the detection of *Mycobacterium tuberculosis* (MTB), isoniazid and rifampicin resistance in acid-fast bacilli smear positive sputum or MTB cultures (FL-LPA), Hain Lifescience, Germany and Nipro, Japan
- Line probe assays for the detection of resistance to fluoroquinolones and second-line injectable agents (SL-LPA), Hain Lifescience, Germany
- TB LAMP for detection of TB, Eiken, Japan

Nonmolecular technologies
- Inteferon gamma release assay (IGRAs) for the diagnosis of latent TB infection (LTBI) Oxford Immunotec, UK, Qiagen, USA

Culture-based technologies
- Commercial liquid culture systems and rapid speciation
- Culture-based phenotypic DST using 1% critical proportion in LJ,7H10,7H11 and MGIT media.

Microscopy
- Light and light-emitting diode microscopy (diagnosis and treatment monitoring)

SCHEDULED FOR WHO EVALUATION IN 2018/19

Molecular detection of TB and drug resistance
- Molecular technologies for genotypic drug resistance testing (including sequencing technologies)
- FluoroType MTBDR, Hain Lifescience, Germany
- *m*2000 RealTi*me* MTB System, Abbott, USA
- BD Max MDR-TB, Becton Dickinson, USA
- Roche cobas® MTB system, Roche Diagnostics, Basel, Switzerland

Radiology
- Computer aided detection (CAD)

WHO POLICY UPDATES SCHEDULED FOR 2018/2019

Molecular detection of TB and drug resistance
- Alere Determine TB-LAM, Alere, USA (TB detection in people seriously ill with HIV)
- Xpert MTB/RIF Ultra for detection of TB and rifampicin resistance in pulmonary, extrapulmonary and paediatric samples, Cepheid, USA

1 Lessem E. The tuberculosis diagnostics pipeline. Treatment Action Group; 2017

1 UNITAID. Tuberculosis – diagnostic technology landscape, 5th edition. Geneva: World Health Organization; 2017

(Reproduced with permission from World Health Organization www.who.int/TB/publications/global_report/en)

1.4.7 Treatment options currently available

The treatment of tuberculous pericarditis is aimed at treating the *Mycobacterium* and the hemodynamic sequelae of the pericardial syndrome.

1.4.7.1 Medical treatment

Treatment of TBP is by use of four anti-tuberculous drugs (Rifampicin, isoniazid, ethambutol and pyrazinamide) for a minimum of 6 months. They reduce the likelihood of developing constrictive pericarditis (Gooi and Smith 1978) and mortality among HIV negative subjects by 8-17% (Bhan 1980). The delay in commencing treatment has been blamed on the difficulty in diagnosis, which may lead to late complications such as constrictive pericarditis and increased mortality. Despite complete treatment, pericardial constriction still occurs, having been reported to commence within two weeks of the bacilli invasion of the pericardium (Föll, Geibel-Zehender, and Bode 2010), thus emphasising the need for prompt diagnosis and commencement of drugs. In a post-hoc study evaluating the effect of the use of anti-TB drugs among cohorts with tuberculous pericarditis, there was an overall mortality rate of 1.43 per 100 person-month in a median follow-up of 11.97 months (Pasipanodya et al. 2015a). Follow-up research reported inadequate antibiotics concentration in the pericardial fluid, with a finding that pericardial fluid rifampicin median peak concentration was lower than the minimum inhibitory concentration (MIC) (Shenje et al. 2015). Also, pyrazinamide peak concentration was 40 times smaller than pH-adjusted MIC, and isoniazid was the only drug that reached pericardial fluid concentration. These findings support the need to investigate alternative drug regimens in patients with EPTB, in whom poor drug penetration may contribute to poor outcome. Others have also expressed concern that the conventional dose of rifampicin (10mg/kg/day) may be too low, for treating both pulmonary TB and EPTB (Chigutsa et al. 2015). The current thinking and direction in the development of new drugs was summarized in the 2018 Global tuberculosis report (Table 1.5).

In the IMPI-1 trial, prednisolone led to a decrease in the rate of pericardial constriction and hospitalisation compared to placebo. However, among HIV positive patients, it was associated with an increased incidence of cancers [1.05 versus 0,32 cases per 100-person-years, hazard ratio 3.27; 95% confidence interval 1.07;10.03. p-value 0.03] (Mayosi et al. 2014).

The same trial also reported that immunotherapy using mycobacterium indicus pranii did not influence the outcome in patients but, instead, increased the incidence of cancers (0.92 versus 0.24 per 100 person-years, hazard ration 3.69, 95% confidence interval 1.03;13.24; p-value 0.03).

A Cochrane systematic review pulling together evidence from 6 trials on interventions for pericarditis, including the IMPI- trial, concluded there was a moderate level of evidence that corticosteroid probably reduced death from pericarditis among HIV negative patients, but that there was little evidence that it can reduce all-cause mortality and the need for pericardiocentesis (Wiysonge et al. 2017). However, for antiretroviral drug naïve HIV positive patients, they found low-level evidence that corticosteroids can reduce constrictive pericarditis and hospitalisation, with no effect on death.

Use of corticosteroid and mycobacterium indicus pranii from the available evidence can increase the incidence of cancer but this conclusion, according to the review, needs further investigation to prove certainty.

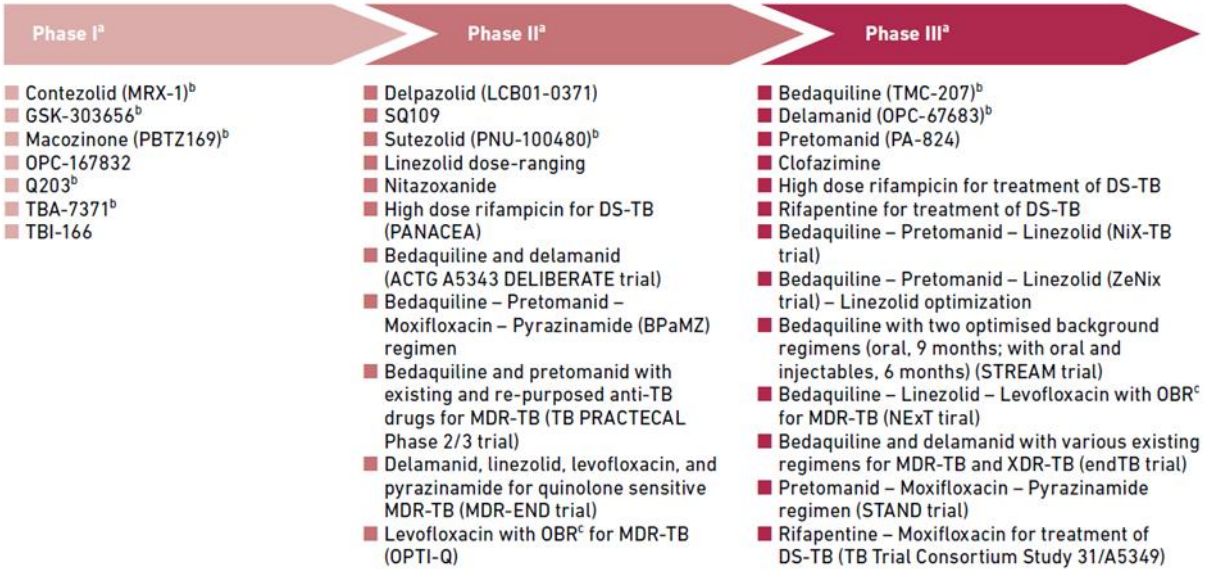
The place of fibrinolysis in pericarditis is the subject of the second investigation of the management of pericarditis (IMPI-2) trial and the pilot study to ascertain the feasibility of this randomised control trial is the focus of this thesis.

1.4.7.2 Invasive management/surgery

Echocardiographic or fluoroscopic guided needle pericardiocentesis is the treatment for cardiac tamponade to drain pericardial fluid. The European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases have proposed a triage system

(Figure 1.4), following the opinion of experts, as a guide on deciding when to intervene and when to transfer the patient to a referral centre (Ristić et al. 2014).

Table 1.5: New anti-TB drugs and regimens in global clinical development pipeline August 2018 (From Global tuberculosis report 2018)



A) Order of listing: New drug compounds, repurposed drugs, regimens.
B) New chemical class.
C) Optimised background regimen.
(Reproduced with permission from World Health Organization www.who.int/TB/publications/global_report/en)

Pericardiocentesis is the most useful therapeutic procedure for early diagnosis and management of cardiac tamponade and symptomatic large pericardial effusion. It is indicated as a necessary emergency procedure even in hemodynamically unstable patients because removal of a small amount of fluid allows normal ventricular filling and restoration of adequate cardiac output (Adler, Charron, Imazio, Badano, Barón-Esquivias, Bogaert, Brucato, Gueret, Klingel, and Lionis 2015). The procedure was first described in 1653 by Napoleon's Physician, Riolanus, as trephination of the sternum to relieve the pericardial compression caused by fluid surrounding the heart (Loukas et al. 2012). The procedure of pericardiocentesis was later (in

1840) explained in the literature by Schur; and the formal description of subxiphoid approach was, for the first time, given in 1911 by Marfan (Marfan 1911; Spodick 1970). For a long time, the procedure was done blindly with associated morbidity and mortality of up to 20% and 6% respectively (Moores and Dziuban 1995; Kil et al. 2008; Nguyen et al. 2011; Ainsworth and Salehian 2011). The introduction of fluoroscopic guidance was later to improve the outcome; however, the advent of ultrasound in the 1970's, popularised by Mayo clinic, remarkably revolutionised the diagnosis and management of pericardial effusion (Tsang et al. 1998; Ball and Morrison 1997). Currently echocardiography guided diagnostic and therapeutic pericardiocentesis is considered the standard clinical practice in the treatment of pericardial effusion (Osranek et al. 2003). It has more than 95% success rate in significant effusion, with a morbidity rate of 1-3% and procedure-related mortality of less than 1% (Nguyen et al. 2011).

Indications for pericardiocentesis include symptomatic moderate to large effusion not responding to medical therapy, suspected tuberculous, bacterial or neoplastic effusion for diagnosis, chronic (greater than three months) large effusion more than 2mm in size at the end of diastole (Adler, Charron, Imazio, Badano, Barón-Esquivias, Bogaert, Brucato, Gueret, Klingel, Lionis, et al. 2015). Contraindications include aortic dissection and post-infarction rupture of the free wall (though it can still be used as a bridge where no immediate surgical management is available to maintain blood pressure around 90mmHg) (Cruz et al. 2015). Other relative contraindications include coagulopathy, anticoagulation treatment and thrombocytopenia (platelet count less than 50000/Mm^3).

As already alluded to, the advent of echocardiogram significantly improved the diagnosis of pericardial effusion (Poprawski, Pitisuttitum, and Tansuphasawadikul 2000; Martin et al. 1978; Van Trigt et al. 1993). However, opinions differ on the place of pericardiocentesis in the routine management of pericardial effusion (Krikorian and Hancock 1978; Van Trigt et al. 1993). The procedure has been in existence since antiquity (Marfan 1911; Spodick 1970) but, until lately,

its use remained controversial (Krikorian and Hancock 1978). Proponents point to the simplicity, convenience, avoidance of general anaesthesia and ability to combine it with catheterisation (Kuhn 1976; Hancock 1971). Those opposed to its use argue that routine pericardiocentesis is only justified in patients without hemodynamic compromise, provided it adds relevant diagnostic information or help avoid further complications (Kilpatrick and Chapman 1965a; Fowler 1976; Silber EN 1975).

Other management options preferred due to the ability for closer visualisation and tissue biopsy for diagnosis include subxiphoid pericardiectomy, pericardial window and thoracotomy.

Isolated studies and case reports involving small sample done decades ago have had conflicting conclusions on the diagnostic yield, symptomatic relief and outcome of percutaneous drainage compared to surgical drainage (Callahan, Seward, Nishimura, Miller, et al. 1985; Kopecky et al. 1986a). Some have also compared surgical drainage to pericardiocentesis focusing on diagnostic yield and outcome (Allen et al. 1999). However, these studies were done in developed countries and, to the best of our knowledge, no such studies have been done in Africa and low- and medium-income countries (LMICs) where most of the clinical condition is seen. There has also not been a large-scale randomised control study to evaluate the role of pericardiocentesis in pericardial effusion outcome.

Identification of aetiology of pericardial effusion is usually made by the invasive collection of pericardial fluid or tissue. Indications for invasive procedures such as pericardiocentesis are large or symptomatic effusion, the presence of tamponade, questionable cause of the effusion (Jung 2012).

In situations where aetiology is not precise, clinical clues can aid in providing useful suggestion on possible aetiology. These clinical indices include the size of effusion, the presence of inflammatory signs and cardiac tamponade (Sagrista-Sauleda et al. 2000).

In order to promote adherence of pericardial layers and prevent further accumulation of fluid, prolonged pericardial drainage of up to 30ml/24 hours following pericardiocentesis has been advocated based on expert opinions, retrospective studies and case reports (LeWinter 2014; Ristić et al. 2014).

Sixty per cent (60%) of patients underwent pericardiocentesis in the IMPI-1 trial; there was 4% re-accumulation with the development of tamponade, 8 % progressed to constriction, with about 50% achieving full recovery (Mayosi et al. 2014). One of the conclusions drawn was that offering pericardiocentesis in TBP was a good clinical practice that may reduce the incidence of complications. However, this conclusion requires further investigation by comparing the eventual outcome with the subject who did not have pericardiocentesis.

In the IMPI-1 trial, a subgroup analysis to evaluate if the use of adjunctive steroids made any difference on the composite outcome among patients who had pericardiocentesis compared to those who did not undergo pericardiocentesis; in chapter four of this thesis, the result of the analysis is presented.

In those who already have features of advanced fibrinous TB effusion, pericardiocentesis is usually unsuccessful and pericardiectomy with complete open drainage is the only effective lifesaving procedure (Imazio 2011). Ultimately surgery is the definitive treatment for chronic constriction in the form of pericardiectomy.

Supportive medical therapy can prove favourable in improving the symptoms of congestion in situations where surgery is contraindicated. Anti-inflammatory treatment such as colchicine and NSAIDs have been shown to be useful in cases of transient constriction in leading to resolution of pericarditis (Haley et al. 2004; Imazio, Brucato, et al. 2010). Patients with potentially reversible forms of constriction may be detected by the presence of CRP and imaging evidence of pericardial inflammation by contrast enhancement on CT and CMR. In

such instances, empiric anti-inflammatory therapy should be considered and may prevent the need for pericardiectomy.

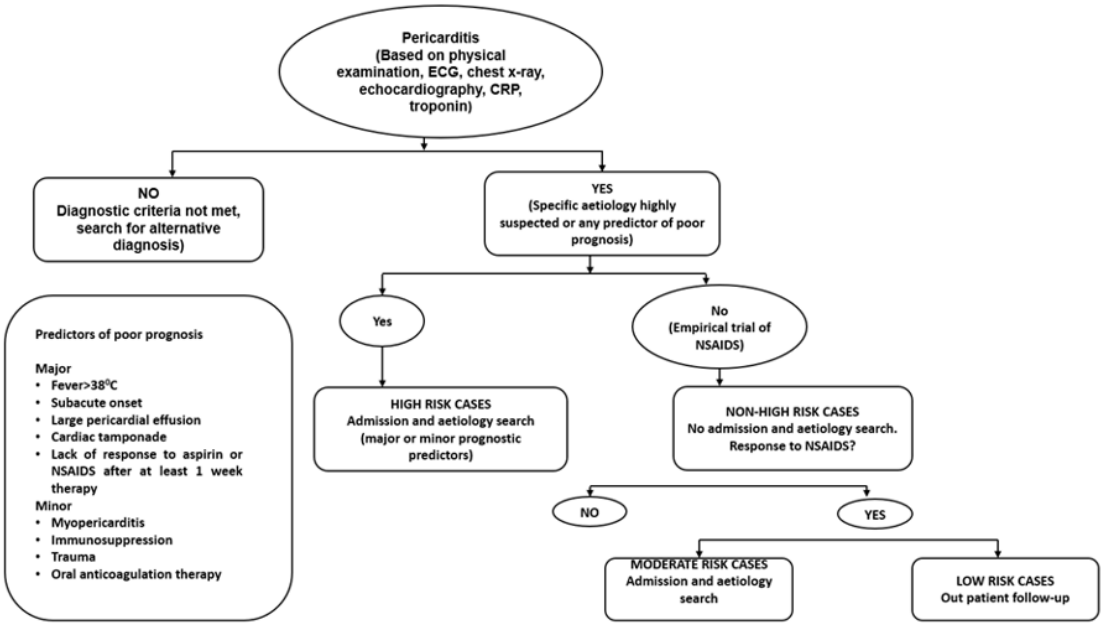


Figure 1.3: Triage of diagnosing pericarditis

(Reproduced with permission from Oxford University Press, first published in the 2015 European Society of Cardiology guideline for diagnosis and management of pericardial disease. published in European Heart Journal 2015, 36; 2921)

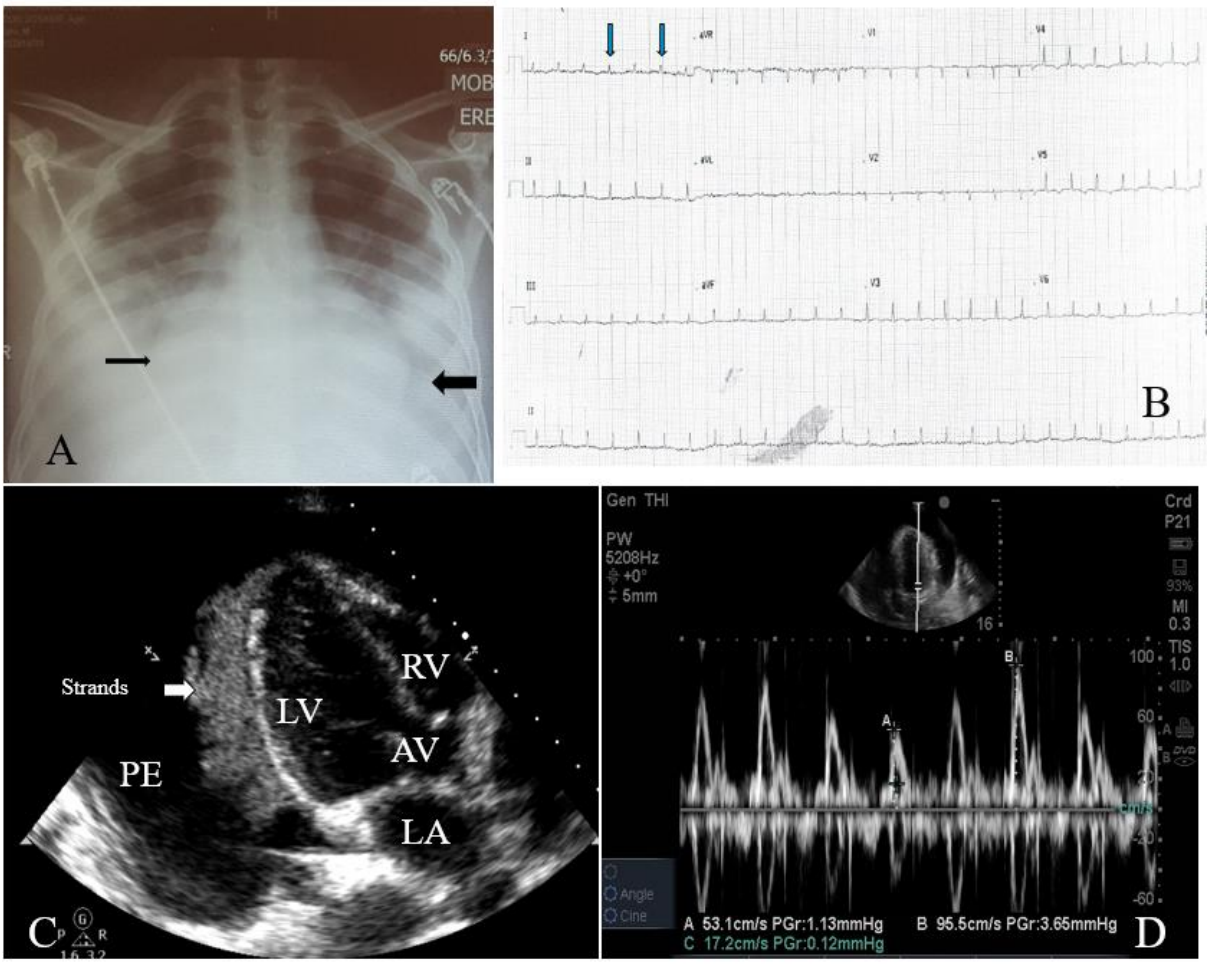


Figure 1.4: 21-year old HIV negative young-man that presented in cardiac tamponade. **A** CHEST X-ray showing globular heart; **B** ECG with tachycardia and low QRS complexes (arrows); **C** 2D echo showing fibrinous large pericardial effusion; **D** Doppler flow tracing of same patient showing mitral E wave inspiratory (A) vs expiratory (B) variation >25%.

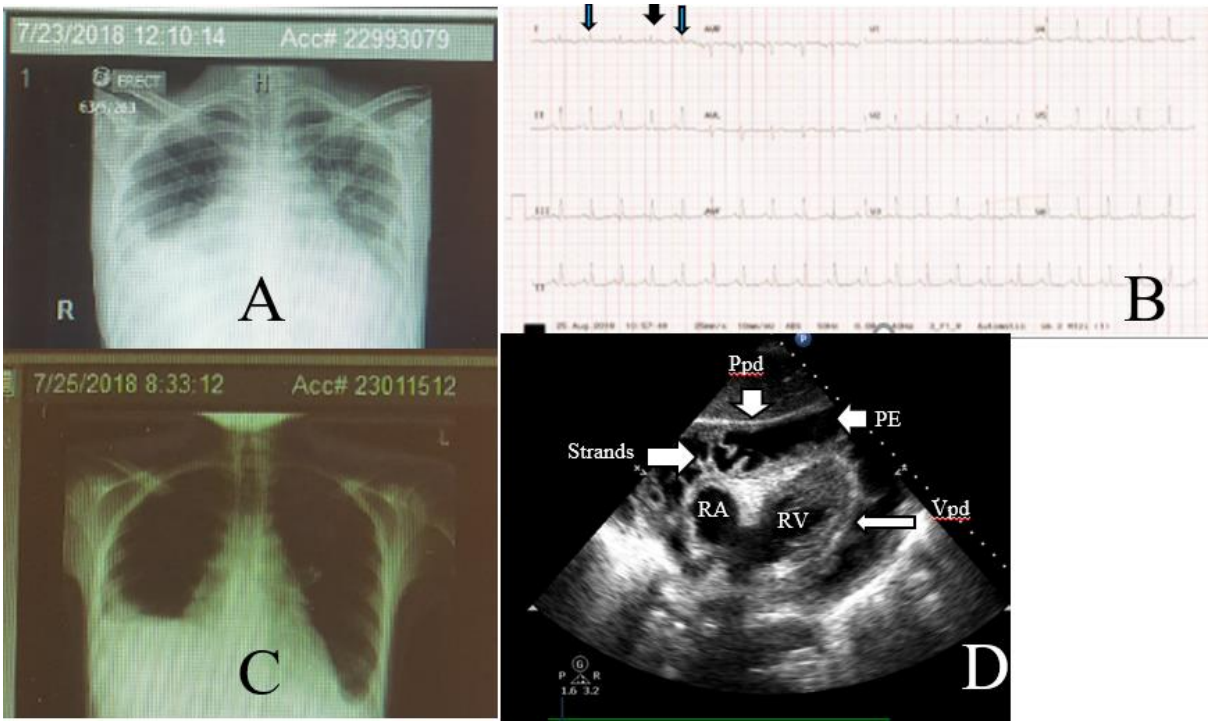


Figure 1.5: 24-year-old RVD positive young lady who presented in cardiac tamponade. **A** Chest x-ray at presentation showing globular heart shadow; **B** ECG, black arrows showing low QRS complexes with electrical alternans; **C** 2D chest x-ray images post pericardiocentesis; **D** 2D echocardiogram with large pericardial effusion [PE], with fibrinous strands, Vpd-visceral pericardium, Ppd- parietal pericardium, RA- right atrium, RV-right ventricle

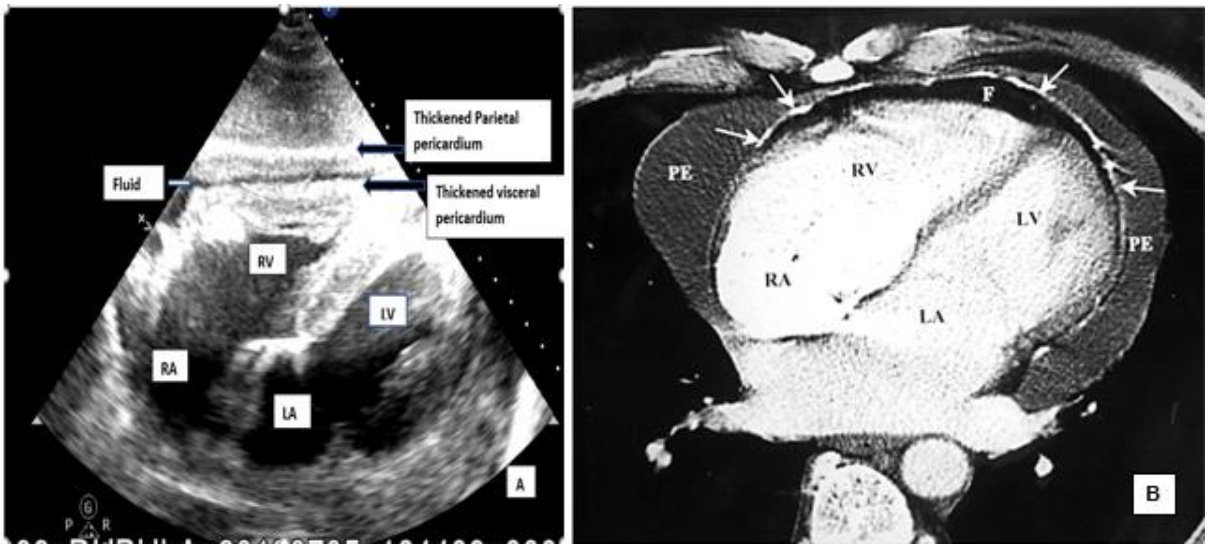


Figure 1. 6: **A** 2D echocardiography image of a 56-year old patient with tuberculosis who presented with evidence of effusive-constriction; **B** MRI image of effusive-constriction (F-fat pad, LA-left atrium, LV-left ventricle, PE-pericardial effusion, RA- right atrium, RV-right ventricle. (Figure B with Copyright © permission of BMJ Publishing Group Ltd & British Cardiovascular Society. Mauro Santarone et al. Heart 2000; 83:556).

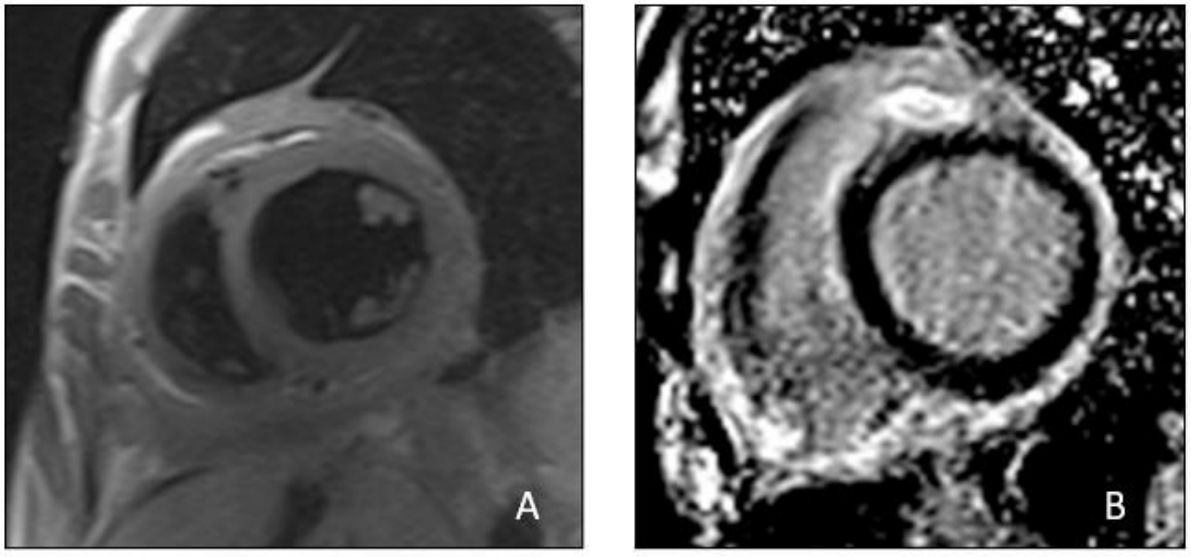


Figure 1.7: Cardiac magnetic resonance images in TB pericarditis. (A) shows T2 weighted STIR imaging with thickened visceral and parietal pericardium and (B) shows fibrotic pericardial layers after administration of gadolinium (Reproduced with permission of Professor Ntusi NAB, et al. J Cardiovasc Magn Reson 2016;18(Suppl1): Q29.)

1.5 Summary of first *I*nvestigation of the *M*anagement of *P*ericardit*i*s Trial (IMPI-I) and its relevance to IMPI-2

Tuberculous pericarditis is a cause of cardiac mortality, especially in areas with high TB burden. Despite use of anti-tuberculosis treatment case fatality rate is up to 26%. The use of corticosteroids may reduce incidence of morbidity from cardiac tamponade and constrictive pericarditis and mortality, while immunotherapy by use of mycobacterium indicus pranii can aid cure in TB.

The concept of the role of inflammation in the pathogenesis of pericarditis leading to constrictive pericarditis has been entertained over the decades. The research into how glucocorticoids can ameliorate the host inflammatory response in TBP and prevent the development of constriction was first documented in 1959 (Schrire 1959). In the study among 28 patients, each group of 14 had either TB drugs with high dose steroid or only TB drugs, no difference was noticed in the two groups.

The first investigation of the management of pericarditis trial (IMPI-1) was designed to investigate the efficacy and safety of adjunctive steroid and immunotherapy in patients with tuberculous pericarditis. The rationale for the trial was based on a number of observations and findings from other studies.

(i) Reduction in occurrence of constrictive pericarditis and mortality following use of adjunctive steroid (Evans 2008; Mayosi 2002; Ntsekhe et al. 2003; Critchley et al. 2013).

(ii) The possibility for mycobacterium indicus pranii to reduce reduction in inflammation tuberculosis and increase in CD4 cell count among HIV infected patients judging from its noticed effect in leprosy (Saini et al. 2009; Mathur 2006; Talwar 1999; Nath 1998; Sharma et al. 2005).

(iii) A concern about the safety of steroids because of the possible increased risk of cancers in HIV patients following glucocorticoid use (Elliott et al. 1992; Elliott et al. 2004).

The first phase IMPI-1(2009-2014) was focused on tuberculous pericarditis (TBP), the leading cause of the disease in Africa and many places with high tuberculosis burden. It was a large scale RCT of 1400 patients (recruited from 19 hospitals from 8 African countries) with TBP randomised to 120mg of adjunctive steroid over six weeks, 5 doses of immunotherapy with subcutaneous injection of mycobacterium indicus pranii over three months or placebo (Mayosi et al. 2014).

A total of 1400 participants were enrolled for comparison of prednisolone with placebo (706 in intervention arm and 694 in placebo, while 1250 participants were enrolled for comparison of mycobacterium indicus pranii with placebo (625 in each arm).

Use of steroid and immunotherapy did not affect the combined primary outcome of all-cause mortality, cardiac tamponade requiring pericardiocentesis and pericardial constriction. Both therapies led to increased incidence of HIV-associated malignancies in those with very advanced immune suppression not on anti-retroviral medications. However, secondary outcome of the rate of constriction was reduced by 46% irrespective, of the HIV status without translating to a reduction in mortality.

Given that the effect of adjunctive therapy on the primary outcome in the trial was neutral, the ESC 2015 guidelines for diagnosis and management of pericardial disease puts the use of steroids in HIV negative patients on TBP in a class 2b level of evidence recommendation(Adler, Charron, Imazio, Badano, Barón-Esquivias, Bogaert, Brucato, Gueret, Klingel, Lionis, et al. 2015). Some authors have argued that subclinical cases of pericardial constriction could have been missed among IMPI-1 cohorts, since diagnosis of

constrictive pericarditis in most of the recruiting centres was based on clinical findings and use of such confirmatory modalities like Tissue Doppler imaging was not (*Kyriakakis 2016).

The neutral result of IMPI-1 trial on the primary efficacy outcome, demands further search for interventions that can lead to reduction of adverse events in tuberculous pericarditis among our patient population. The second investigation for management of pericarditis (IMPI-2) trial is in answer to this quest. However, it will involve both tuberculous and non-tuberculous pericarditis and is set to investigate if the use of fibrinolysis can lead to a reduction in the primary outcome of persisting pericardial effusion leading to tamponade and pericardial constriction. The feasibility of the RCT to evaluate this question is the reason for the IMPI-2 pilot study and one of the central themes in this thesis.

1.6 The role of fibrinolysis in pericarditis

More than 60 years ago physicians employed the use of intra-pericardial fibrinolysis in the management of purulent pericardial effusion as rescue therapy after other management failed (Adie and Childress 1951b; Wright et al. 1951). However not much was seen in the literature again on its use until in the 1980s when it was revisited (Bennett 1984). Following those documentations, there have been isolated case reports alluding to its role, both in humans and animal studies (Dybowska et al. 2015; Bigham et al. 2008).

In exudative pericarditis such as post pneumonia and tuberculosis, the formation of fibrinous strands can lead to loculation. Use of fibrinolysis can, therefore, help in breaking these and allow complete evacuation. Open surgical drainage under general anesthesia with its attendant risk is usually the definitive way of managing persistent pericardial effusion to prevents its sequelae of constrictive pericarditis. However, the use of intra-pericardial fibrinolysis can be an effective and safe intervention in this condition.

A randomised control trial among 94 Chinese patients with tuberculous and purulent effusion

concluded that early administration of intra-pericardial urokinase led to complete drainage and reduction in progression to pericardial constriction (Cui et al. 2005). A 2011 review of studies on the use of fibrinolysis in purulent pericarditis concluded that among 40 patients, there was a failure of pericardiocentesis requiring pericardiectomy in 2 patients, while in 36 patients with data, no constriction was found (Augustin et al. 2011).

The concept of fibrinolysis to facilitate drainage is premised on the observation that inflammatory insults to the pericardial space attract leucocytes which, upon activation lead to the promotion of coagulation with resultant fibrin deposition (Figure1.1). The formation of fibrin bands limits the free flow of pericardial fluid during drainage because of adhesions, thus causing loculation. Results from experimental models have been used to show that fibrin deposition form the cornerstone of the pathogenesis of inflammatory pericarditis and constrictive pericarditis and so is a potential target in inflammatory pericarditis such as tuberculosis, purulent and malignant effusion.

1.6.1 The pharmacology of fibrinolysis.

Plasmin is a cleaved product formed by activation of plasminogen by thrombolytic drugs leading to clot dissolution. (Figure 1.8). It a proteolytic enzyme with the ability to break cross-links between fibrin molecules, responsible for the structural integrity of blood clots. This property of thrombolytic drugs is the reason why they are also referred to as "plasminogen activators" and "fibrinolytic drugs."

Intrapericardial streptokinase has been the more frequently used agent although both urokinase and tissue plasminogen activator (t-PA) have also been used in pericardial fibrinolysis, with the latter two preferred due to lower risk of allergy. Other disadvantages of streptokinase include antibody formation, longer half-life, systemic thrombolysis due to the

creation of a complex with plasminogen and more complex dosing regimen.

Natural occurring t-PA is a serine protease that converts the zymogen plasminogen into active serine protease plasmin, an enzyme responsible for removal of fibrin deposits. It drives intravascular fibrinolysis, and parenteral alteplase (recombinant t-PA) administration significantly increases t-PA concentration in plasma. It has a half-life of <5 minutes and binds to activated fibrin before binding to plasminogen. Different dosing regimen has been used from 2mg to 50mg in the literature (Rahman et al. 1998; Bigham et al. 2008; Reznikoff, Fish, and Coursin 2003) with suggestions on retaining the drug for some time to aid distribution in the pericardium.

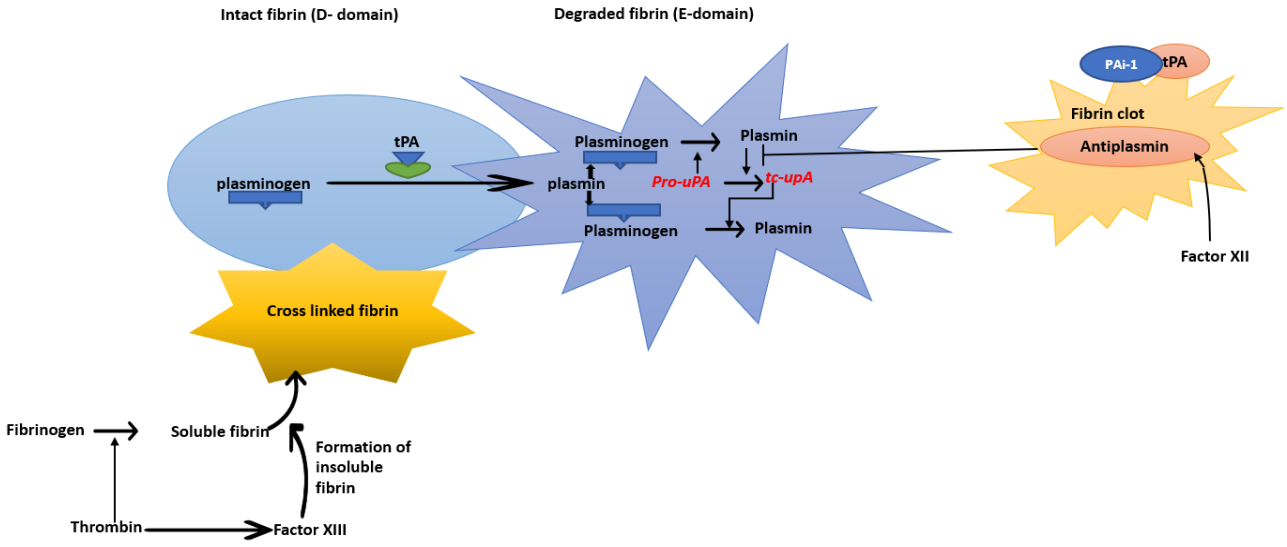


Figure 1.8: Fibrinolysis pathway (t-PA: tissue plasminogen activator; pro-uPA: proenzyme form of urokinase plasminogen activator; tc-uPA: active form of urokinase plasminogen activator; PAI-1: plasminogen activator inhibitor-1)

1.6.2 Adverse events of intra-pericardial Fibrinolysis

Following repeated instillation of streptokinase, there could be allergic reactions, and this is a

well-known complication of fibrinolysis. However, treatment with urokinase or t-PA greatly reduces this risk (Augustin et al. 2011). There have been concerns with intra-pericardial bleeding. However, there has been only one case of haemorrhagic tamponade after fibrinolysis reported in the literature (Juneja et al. 1999) and may not be directly related to fibrinolysis. Bleeding events are not common with fibrinolysis for empyema in published case reports (Cameron and Davies 2008; Diacon et al. 2004) and studies from coagulation laboratories show that there is no proven systematic effect when fibrinolysis is used in purulent pericarditis (Ustunsoy et al. 2002). Cardiac tamponade is the other risk which can theoretically occur if the pericardial drain does not evacuate all the instilled volume. The addition of a small quantity of liquid may provoke cardiac compression (Refsum et al. 1981). However, no tamponade due to the intra-pericardial administration of fibrinolytic agents has been described (Augustin et al. 2011). The risk of tamponade could be lowered if the volume of fibrinolytic agent instilled is less than the amount of fluid drained immediately beforehand.

Potential benefits of intra-pericardial fibrinolysis seem to outweigh the apparent low morbidity associated with the procedure based on case reports and a small clinical trial.

1.7 The second Investigation of Management of Pericarditis Trial (IMPI-2)

The second investigation of the management of pericarditis (IMPI-2) trial is a randomised controlled trial focused on the use of intrapericardial alteplase to facilitate complete drainage when indicated in patients with large pericardial effusion compared to routine care. The study will provide a definitive answer to the question of the use of fibrinolysis. In chapter 5 of this thesis, the proof of concept and feasibility study of the RCT is presented.

CONCLUSION

In this introductory chapter, we have highlighted the essential position pilot trials occupy in

planning for a randomised control trial; showing that if painstakingly designed and carried out, they can help refine and facilitate smooth conduct of all aspects of the main trial. Methodological reporting of the pilot studies is also an essential obligation with the potential of not only projecting such small works but can create awareness among researchers and help change the attitude of journal editors in the publishing of pilot trials.

Subgroup analysis, another essential tool in unearthing non-obvious findings of RCT was also reviewed in the chapter, highlighting the criticisms and strengths of in their conduct. Subgroup analysis should be predefined at the design stage before the commencement of RCT to avoid bias and data mining; the results of such analysis should also be presented with caution.

An overview of tuberculous pericarditis a significant cause of pericarditis in Africa was also discussed in this chapter; culminating in the review of the first investigation of the management of pericarditis trial in Africa (IMPI-1). The section discussed the rationale for the conduct of IMPI-1 trial, the summary of the trial results and why it was necessary to explore the question of interventions to reduce adverse events in pericarditis further through the second RCT (IMPI-2 trial). The second investigation of the management of pericarditis trial focuses on the place of intrapericardial fibrinolysis in facilitating complete aspiration compared to conventional pericardiocentesis in adults with large pericardial effusion. So, in the last section of the chapter, the place of fibrinolysis in pericarditis is discussed. All the issues covered in this introductory chapter will shape the subsequent sections of the thesis.

In chapter 2 and 3, the CONSORT extension for reporting of pilot trials is introduced in line with the objectives of the developers to aid reporting of pilot trials. This section of the thesis leverages on the concept to x-ray reporting of pilot trials in heart failure in order to improve the conduct and reporting of the IMPI-2 pilot trial presented in chapter 5.

CHAPTER TWO
Systematic Survey of Reporting Quality of Pilot Trials Protocol (Presented as a Published Manuscript)

2.1 Introduction

Scientific research publications have contributed enormously to improving the diagnosis and management of diseases. The gold standard for these researches is an appropriately designed, conducted and reported randomized control trial (RCT), as they usually function as the factory of breakthroughs in the biomedical world. However, often these trials result in failure and a monumental waste of resources, time and loss of unintended lives because of poor reporting.

Wrongly reported RCTs can lead to bias and misleading results, conclusions, interpretations, and inferences with its attendant consequences to both patients and society in general. This has been the fate of some RCTs in the past and such happenings can be blamed on lack of methodological rigour (Ntala et al. 2013). The need to address such unfortunate problems led to the development of the consolidated standard for reporting of trials (CONSORT) checklist in 1996 (Moher et al. 2010) which has since then undergone two revisions in 2001 and 2010 (Begg et al. 1996; Moher et al. 2010). The introduction of the CONSORT checklist, as attested to by some major journals, have led to standardization and improvement in the quality of reporting (Devereaux et al. 2002; Moher, Jones, and Lepage 2001; Plint et al. 2006).

The CONSORT checklist initially intended for guidance on reporting of all types of RCTs, was not entirely applicable to most earlier phase trials and others such as cluster randomized trials and non-inferiority trials which require additional information (Schulz, Altman, and Moher 2010). This led to the extension in the CONSORT checklist to accommodate trials that are not large, parallel arm clinical investigations (Dolgin 2013).

However, pilot trials which are an important prerequisite for the conduct of higher quality RCTs have not been addressed by available extensions. Evaluation of published pilot trials have consistently concluded that pilot trials are poorly reported due mainly to inappropriate focus (Arain et al. 2010b; Lancaster, Dodd, and Williamson 2004b; Shanyinde, Pickering, and Weatherall 2011), fuelling the fear that this important arm of research that provides information on the feasibility or otherwise of planned bigger studies run the risk of getting lost or redundant, a potentially disastrous consequence for clinical research (Thabane et al. 2010).

In 2016, the CONSORT group introduced an extension for pilot and feasibility trials (Eldridge S 2016), to ensure accurate design conduct and reporting of pilot trials (Charlesworth et al. 2013; Lancaster 2015).

The second randomized controlled trial on the investigation of the management of pericardial disease (IMPI-2) trial, is a trial on the use of intrapericardial alteplase to facilitate complete aspiration compared to routine care in patients with large pericardial effusion. It is designed to be preceded by a pilot trial as a preparatory phase to evaluate the feasibility of the multicentre main study. This thesis uses the experience gained in the processes of the IMPI-2 pilot trial to discuss the role feasibility studies play in cardiovascular research.

There is a need to lay a solid foundation for the main study by learning from what has been done previously and to improve on them. To do this, we started by doing a systematic survey of the quality of pilot trials focusing on heart failure, due to its central role in cardiovascular disease, and the volume of trials it has recorded. In this chapter, we present the first phase of this evaluation (on abstracts) of quality of report in the form of publications. This chapter is a published protocol for the systematic survey.

2.2 Publication Review

The publication describes the protocol of a systematic survey on heart failure pilot trials abstract. It gives the step-by-step account of the process and how we arrived at the selected publications. It also provides the rationale for choosing the CONSORT checklist for the assessment of the quality of reporting.

2.2.1 Contribution of paper to the thesis novelty

The survey provided the opportunity on skills to identify pilot trial publications, evaluate the methodology and questions asked. In developing the protocol, the general knowledge of processes in a pilot trial was gained in preparation for the IMPI-2 pilot trial. The teamwork also was a dress rehearsal for the administrative challenges of managing the trial team.

2.2.2 Role of the candidate

I was responsible for development and refining of the concept, designing of data extraction tool, conduction of the literature search, selection of eligible manuscripts for the survey and drafting/editing of the manuscript for publication.

2.2.3 Roles of the co-authors

LT and BM originated the idea, edited the manuscript at each stage, and approved the final draft for publication. LT was the guarantor and provided support and intellectual discuss at each stage.

MZ and GC jointly drew up the process of paper review for eligibility and data abstraction. MZ reviewed the draft for scientific content. MC did the statistical work for the manuscript.

2.2.4 Publication status

The manuscript was published in 2017 in a peer review journal.

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Quality of abstracts of pilot trials in heart failure: A protocol for a systematic survey

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ABSTRACT

Introduction: Pilot trials are initial small-scale studies done to inform the design of larger trials. Their findings like other studies are usually disseminated as peer-reviewed journal articles. Abstracts are used to introduce the contents to readers and give a general idea about the full reports and sometimes are the only source of in- formation available to readers. Despite their importance, the contents of abstracts of trial reports are usually not informative enough and lack the essential details.

Methods and analysis: This is a protocol for a planned systematic survey with a primary aim of analyzing the reporting quality measured as the completeness of the reporting of pilot trial abstracts in heart failure. The secondary aim will be to explore factors associated with better reporting quality.

Abstracts of heart failure pilot trials in humans (journal and conference abstracts) published in the English language from 1 January 1990 to 30 November 2016 will be assessed to determine the reporting quality, based on the CONSORT 2010 statement extension to randomized pilot and feasibility trials. All non-pilot/feasibility trials and non-human pilot trials will be excluded. We will search Medline (PUBMED), Cochrane controlled trials register, Scopus and African wide information databases for pilot trials in heart failure. Title and abstracts of identified studies will be screened for inclusion and data extracted independently by two reviewers in duplicate without using the full text. Reported and unreported items on the abstracts will be presented as frequencies and percentages, a descriptive analysis will be used to interpret the reporting quality and regression analysis used for characteristics associated with greater statistical reporting at 95% confidence interval.

Review registration number: PROSPERO CRD42016049911.

1. Introduction

Abstracts are introductory summaries of full text that provide readers with a quick overview of the contents of the papers. They serve as an important aid in knowledge dissemination. Many researchers rely on abstracts as a concise source of information [1], helping them follow developments in the literature [2] and in reaching decisions on what articles to read in detail. Reasons advanced for the essential role of abstracts include the challenge of the large volume of literature, un-availability/inaccessibility of full text to some readers due to high cost [3,4], and the fact that some articles not published in English provide abstracts in English to reach a wider audience. These important roles of abstracts, therefore, require that they contain sufficient and accurate information that will guild the readers into contents of the full text [5].

Pilot trials refer to initial small studies that researchers use in reaching the decision on commencing larger confirmatory trials [6–8]. They are comprised of a distinctive group of randomized controlled trials (RCT) often referred to as pilot and feasibility trials which do not have effectiveness or efficacy as their primary focus [9]. By the nature of their design, they are not powered for hypothesis testing, but rather should emphasize on confidence interval estimation and are usually designed to support the development of a future definitive RCT.

The consolidated standard for reporting of trials (CONSORT) statement (www.consort-statement.org) originated because of the

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concern raised over the years on the quality of report of RCTs [10]. It is a guideline that was designed to improve the quality of reporting, first published in 1996 revised in 2001 and later updated in 2010 [11,12], to address this observation by providing a benchmark for complete reporting of trials. This development has been well received by many peer review journals [13] and has been shown to improve the quality of reporting of trials [14–16].

The noted improvement has led to the extension of the checklist to various other forms of trials such as non-inferiority, equivalence, and cluster or pragmatic designs. There have also been extensions for different types of interventions (non-drug treatments and herbal interventions), Patient-reported outcomes, as well as extensions for re- porting harms. One major characteristic of the main CONSORT statement and all the current extensions is that they focus on trials for which the research question centers on the effectiveness or efficacy of an intervention. But as stated above pilot and feasibility trials are de- signed for a different purpose, serving as a precursor to definitive trials and have been at various times described as a neglected arm of medical research [17]. In order to improve reporting of pilot and feasibility trials, a group of researchers recently developed a checklist extension to serve this function [18].

In this paper, we present a protocol for a systematic survey of quality of reporting in abstracts of pilot trials in heart failure, aimed at evaluating the completeness of such reports based on the checklist ex- tension. For the purpose of the survey, heart failure is defined as a clinical condition often referred to as congestive heart failure (CHF), which occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs [19]. We will be reviewing ab- stracts of journal publications and conferences focusing on all types of heart failure. We chose heart failure for this survey because of its role in the global burden of cardiovascular diseases [20,21] and the large volumes of trials in heart failure.

In the last two decades, an increasing number of clinical trials in cardiovascular disease (CVD) have been conducted mainly due to the rising prominence of CVD as one of the leading causes of morbidity and mortality [21]. A sizable number of these clinical studies were preceded by pilot trials and their results disseminated to the public through publications. However, these pilot studies were not exempt from the inconsistency in quality reporting of most of the randomized control trials (RCT). The quality of reporting across journals is variable with some journal abstracts communicating adequate information and some grossly insufficient for accurate interpretation [22]. The correct interpretation of abstracts can be enhanced if the reporting of the study design, methods, and results are complete and uniform across journals [23,24]. Similarly, a structured and detailed reporting of RCT helps guideline developers and policy makers as they rely on RCTs [24,25].

Incomplete information which may follow using a very small sample or not well-defined outcomes [26,27] make it difficult to trust the findings resulting in suboptimal use of these RCTs [28]. Other factors that have also been reported to influence the quality of report of trials include multi-center studies, trials involving pharmacological studies, industrial sponsored studies and those reporting positive results for their primary outcome [29]. Hence, it is imperative for authors to report complete details of their research and for journals to ensure proper reporting is adhered to by authors.

The primary hypothesis in the planned systematic survey is that the quality of reports in abstracts of pilot trials in heart failure based on the CONSORT checklist extension for pilot and feasibility trials is poor. The exploratory hypothesis is that items in CONSORT extension for reporting of pilot trials will be seen more in publications that contain the characteristics mentioned above.

2. Methods and analysis

2.1. Primary Objective

To evaluate the reporting quality of abstracts of pilot trials in heart failure in the past 26 years (1990–2016), using CONSORT extension for reporting of abstracts of pilot trials as the reference standard.

2.2. Secondary Objectives

1 To identify aspects of the checklist consistently reported in pilot trials
2 To identify factors associated with proper reporting of abstracts of pilot trials

2.3. Inclusion criteria

Type of studies: pilot/feasibility heart failure trial with a randomized control design (parallel or cluster) done in humans, Participants: reports on population with heart failure,
Intervention: pharmacological and non-pharmacological interventions evaluating clinical outcomes,

- Publications from 1st January 1990 to 30 November 2016.

2.4. Exclusion criteria

- Non-pilot trials in heart failure,
- Animal studies.

2.5. Study design

The proposed survey will involve a systematic review of a sample of abstracts from all available publications on pilot trials in heart failure published from January 1990 to November 2016. We will systematically search Medline (PUBMED), Cochrane controlled trial register, Scopus, and African wide information electronic databases using search terms and medical subject headings (MESH) to identify heart failure pilot trials investigating pharmacological and non-pharmacological interventions (Table 1 and Appendix A). Articles will be restricted to those written in the English language.

Table 2.1
Medline search strategy.

(((((Heart failure[MeSH Terms]) OR ((Heart failure OR paroxysmal dyspnea OR diastolic heart failure OR systolic heart failure OR Cardiac Failure OR Heart Decompensation OR Myocardial Failure OR Congestive Heart Failure OR Ventricular dysfunction OR cardiac insufficiency OR myocardial failure OR myocardial insufficiency)))) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR (comparative study) OR (comparative studies) OR (evaluation studies) OR (evaluation study) OR follow-up studies [mh] OR prospective studies [mh] OR controlled [tw]OR controls [tw]OR control [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])))))) AND (((Pilot projects[MeSH Terms]) OR Feasibility Studies[MeSH Terms]) OR ((pilot OR feasibility)))

Table 2.2
Estimation of sample size based on 95% Confidence Interval.

		P_0									
		0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95
E	0.01	9604	9507	9219	8739	8067	7203	6147	4898	3457	1824
	0.05	384	372	368	349	322	288	245	195	138	73
	0.10	96	95	92	87	80	72	61	49	34	18

P_0 = Prior estimate of studies with adequate reporting. E = Margin of error for the estimate.

3. Data extraction and synthesis

Selected articles based on the key search words of pilot trials in heart failure from 1990 to 2016 will be exported to Endnote X7® reference manager software; duplicates will be identified and removed. Screening and data abstraction will be done independently and in du- plicate by two reviewers (GI and MZ) using a customized data extraction form in Microsoft Excel® format. Reviewer agreements will be measured using kappa statistics [30]. Discrepancies and differences of opinion will be resolved by consensus between reviewers or arbitration by a third reviewer. The abstracts (both journal and conference) will be evaluated using the 16 items of the CONSORT extension (Appendix B); where the item combines two or more pieces of information (e.g. eligibility and setting), each will be counted separately if it can stand alone. Where they are open to interpretation, the reviewers' interpretation of relevant information will be used. Reported items will be checked as yes and unreported items as no. Non-applicable items will be checked as NA. All "yes" responses will be assigned the number 1, while "no" and NA will be assigned 0. The overall quality of the ab- stracts will be calculated as a proportion of y e s .

3.1. General characteristics

Information to extract from the publications will include names and addresses of authors, journal names, impact factor, Journal policy on the endorsement of CONSORT statement (by checking on the website of the journal), year of publication.

3.2. Assessment of abstract using CONSORT extension for pilot and feasibility trials checklist

Title identification as trials will be checked, and abstract format noted as structured or unstructured. Trial design (Cluster/parallel), participant's characteristics such as eligibility and setting of pilot trial conduct, type of intervention in each group, Single or multiple centers, as well as defined pre-specified objectives. Other things to be checked will include pre-specified measurements to determine the outcome, method of randomization and blinding, the number of participants screened and randomized. There will also be an evaluation of analysis done in each group including study outcome, explanation of harm re- porting and general interpretation of result discussing risk and benefit. Finally, we will check the conclusions drawn from the study, implications for future definitive trial, trial registration and funding information.

4. Definition of adequate reporting

The CONSORT extension for reporting of abstracts has 16 items which are expected to be in an abstract. In this survey, a publication abstract will be judged as adequate if all the items are reported.

Table 2.3

Objectives	Outcome	Explanatory Notes	Hypothesis	Method of analysis
Primary: To review the quality of abstracts of pilot trials in heart failure in the past 26 years (1990–2016), using CONSORT extension for	1 Overall quality of the reporting of abstracts 2 Quality of reporting of the individual items	Publications done from January 1990 to November 2016 1 CONSORT endorsement by the journal 2 Number of centres (single vs. Multi-centric) 3 Type of intervention (pharmacological vs. Non-pharmacological) 4 Significance of results for primary outcome	The quality of reporting of abstracts is suboptimal	1 Presented as frequencies and percentages using descriptive analysis. Poisson regression analysis (or negative binomial regression) to present factors related to reporting at 95% CI
Secondary: 1 Identify aspect of checklist consistently reported in pilot trials, 2 Identify factors associated with good reporting of abstracts of				2 Regression analysis

4.1. Sampling scheme and sample size calculation

We will consider for inclusion in the systematic survey, all sampled studies described as pilot or feasibility randomized control trials (RCT) from the general sampling population of RCTs in heart failure. Eligible trials will be those done in humans from 1 January 1990 to 30 November 2016 and reported in the English language. Nonrandomized trials and crossover studies will not be included in the survey. For purposes of the survey, adequate reporting of abstract will be determined by considering the proportion of studies reporting up to 16 items in the checklist. Using a 95% confidence interval approach, the number of required pilot trials abstracts (n) for the survey will begiven by:

$$n \quad 1.962(P_0\,(1 \quad P_0)/E^2)$$

where 1.96 is the z-score associated with a 95% confidence interval, P_0 is the prior estimate of the proportion of studies with adequate reporting of abstract and E is the target margin of error for the estimate. With a margin of error of E = 0.10, our expectation is that the number of studies with an adequate report of abstracts will be calculated at P_0 = 0.60 [31,32] (Table 2).

4.2. Statistical analyses

As shown in Table 3, the analysis will be divided into two sections.

4.2.1. Primary outcome measures

Reporting quality by presenting reported and unreported items on the checklist as frequencies and percentages using descriptive analysis.

4.2.2. Secondary outcome measures

Negative binomial regression analysis will be used to determine the study characteristics associated with greater statistical reporting. Count of adequately reported items on the checklist will be the dependent variable. The independent variable will include the following characteristics linked to reporting quality in previous publications [11,23,24,26,27,29]; journal impact factor, endorsement of CONSORT, sample size, single or multiple sites, type of study (pharmacological or non-pharmacological), abstract format (structured or unstructured). Incident risk ratio (IRR) will be calculated to evaluate factors associated with better reporting. The result will be presented as IRR with 95% confidence interval and associated p-values. The criterion for statistical significance will be set at alpha = 0.05. We will use SPSS software version 23 (Chicago, IL) for all analyses.

5. Ethics and dissemination

Formal ethical approval is not required for the proposed survey as data collection is based on publicly available reports. This protocol was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Protocols (PRISMA-P) [33]. We will submit this systematic survey when completed to a peer-re- viewed journal for publication, and the findings will also be presented at an upcoming conference.

6. Discussion

This planned systematic survey of quality of abstracts of pilot trials was registered prospectively in PROSPERO (CRD42016049911) and the protocol was written in line with PRISMA-P. It is to the best of our knowledge the first of such review using the CONSORT extension for reporting abstracts of pilot trials. The heart failure trials to be analyzed were published before the introduction of the CONSORT extension. However, the work will serve as the basis to evaluate improvement when the extension is fully in operation.

7. Authors' data sharing and contributions

All authors contributed to the protocol and approved the final manuscript. LT and BM were responsible for the conception of the survey. GI was involved in the search strategy. GI and LT designed the survey. GI, MZ, MC were involved in designing and testing of the data extraction form. GI wrote the initial draft, GI and LT contributed to improvements in the manuscript and BM and LT critically revised the final draft.
All authors approved the final written manuscript. Responsibility for statistical analysis Plan: MC.
Guarantor of the systematic survey; Prof. Lehana Thabane.

8. Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

9. Competing for interests' statement

The authors do not have any competing interests to report.

Appendix A

Heart failure Pilot Trial Search Strategy.

PubMed search

Heart failure [Mesh] OR.
Heart failure OR paroxysmal dyspnea OR diastolic heart failure OR systolic heart failure OR Cardiac Failure OR Heart Decompensation OR Myocardial Failure OR Congestive Heart Failure OR Ventricular dysfunction OR cardiac insufficiency OR myocardial failure OR myocardial insufficiency.
AND.

Filters for RCT's in PubMed courtesy University of Cape Town Library

Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double- blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR (comparative study) OR (comparative studies) OR (evaluation studies) OR (evaluation study) OR follow-up studies [mh] OR pro- spective studies [mh] OR controlled [tw]OR controls [tw]OR control [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])
AND.

Pilot projects [MeSH] OR Feasibility Studies [MeSH] OR pilot OR feasibility. Filter by years.
Filter by years (1 January 1990–1 May 2016)

Africa-Wide (Ebsco) and Web of Science

Heart failure OR paroxysmal dyspnea OR diastolic heart failure OR systolic heart failure OR Cardiac Failure OR Heart Decompensation OR Myocardial Failure OR Congestive Heart Failure OR Ventricular dysfunction OR cardiac insufficiency OR myocardial failure OR myocardial insufficiency.
AND.
Clinical trial OR randomized controlled trial OR randomized controlled trial OR random allocation OR double-blind OR single-blind OR placebo OR random research OR comparative study OR evaluation study OR follow up OR follow-up OR prospective OR control OR volunteer OR single mask OR double mask OR treble mask OR triple mask OR single blind OR double-blind OR treble blind OR triple blind.
AND.
Pilot OR feasibility.
Filter by years (1 January 1990–1 May 2016)

Scopus-

Heart failure OR paroxysmal dyspnea OR diastolic heart failure OR systolic heart failure OR Cardiac Failure OR Heart Decompensation OR Myocardial Failure OR Congestive Heart Failure OR Ventricular dysfunction OR cardiac insufficiency OR myocardial failure OR.
Myocardial insufficiency.

AND

Clinical trial OR randomized controlled trial OR randomized controlled trial OR random allocation OR double-blind OR single-blind OR placebo OR random research OR comparative study OR evaluation study OR follow up OR follow-up OR prospective OR.
Control* OR volunteer OR single mask OR double mask OR treble mask OR triple mask OR.
Single-blind OR double-blind OR treble blind OR triple blind AND pilot OR feasibility.

Appendix B. CONSORT extension for reporting abstracts of pilot trials [9]

Item	Extension for pilot trials	Judgment Yes	Judgment No	Score
Title	Identification of study as a randomized pilot trial			
Trial Design	Description of pilot trial design (e.g. parallel, cluster			
METHODS				
Participants	Eligibility criteria for participants and the settings where the pilot trial was conducted			
Interventions	Interventions intended for each group			
Objective	Specific objectives of the pilot trial			
Outcome	Pre-specified assessment or measurement to address the pilot trial objective(s)[1]			
Randomization	How participants were allocated to the interventions			
Blinding (masking)	Whether or not participants, caregivers, and those assessing the outcomes were blinded to group assignment			
RESULTS				
Numbers randomized	Number of participants screened and randomized to each group for the pilot trial objective(s)[1]			
Recruitment	Trial status[2]			
Numbers analyzed	Number of participants analyzed in each group for the pilot objective(s)[1]			
Outcome	Results for the pilot objective (s); including any expressions of uncertainty[1]			
Harms	Important adverse events or side-effects			
Conclusion	General interpretation of the results of pilot trial and their implications for the future definitive trial			
Trial Registration	Registration number for pilot trial and name of trial register			
Funding	Source of funding for pilot trial			

[1] Space permitting, list all pilot trial objectives and give the results for each. Otherwise, report those, which are a priori, agreed as the most important (main) to the decision to proceed with the future definitive trial.
[2] For conference abstracts.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2017.11.004.

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CHAPTER THREE
Result of Systematic Survey on Quality of Pilot Trial Abstracts in Heart Failure (Presented as a Published Paper)

3.1 Paper Review

In this publication we present the findings of the first part of our survey on the quality of heart failure pilot trials, focussing on abstracts. It provided the opportunity to systematically sieve the literature and the experience revealed the details of missing information and how it relates to quality and perception of pilot trials.

3.1.1 Contribution of paper to the thesis novelty

The survey provided the opportunity to find out what is reported in the pilot trials, the processes and challenges in conducting pilot trials, as well as the errors. The experience gained was a good preparation for conducting an IMPI-2 pilot trial and a rich source of information on how to report the findings in order to ensure it guides the development of a definitive trial

3.1.2 Role of the Candidate

I did the data extraction, paper reviews, manuscript development and implementation and incorporation of co-authors inputs. I also was responsible for the production of the final edition of article publication.

3.1.3 Roles of the co-authors

LT and BM provided the intellectual substance and constant supervisory support.

MZ, MC and GC jointly reviewed the papers for eligibility and data abstraction. MZ reviewed the draft for scientific content. MC conducted and wrote up the statistical

LT approved the final edition of the manuscript for publication.

3.1.4 Publication status

The manuscript was published 2018 in a peer review journal.

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Pilot and Feasibility Studies

RESEARCH Open

Quality of pilot trial abstracts in heart failure is suboptimal: a systematic survey

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Abstract

Background: Pilot trials are miniature researches carried out with the sole aim of acting as the precursor for larger more definitive studies. Abstracts are used to summarize and introduce the findings to the reading audience. There is substantive empirical evidence showing that abstracts, despite their important roles, are not informative enough, lacking the necessary details. This systematic survey was designed to assess the quality of reporting of heart failure pilot trial abstracts. The quality of reporting was defined as the completeness of reporting based on adherence to the CONSORT extension for reporting of pilot trial abstracts. We also identified factors associated with reporting quality.

Methods: We searched MEDLINE (PubMed), Cochrane Controlled Trials Register, Scopus, and African-wide information databases for abstracts from heart failure pilot trials in humans published from 1 January 1990 to 30 November 2016. These were assessed to determine the extent of adherence to CONSORT extension checklist for reporting of abstracts of pilot trials. We screened identified studies for inclusion based on title and abstract. Data were independently extracted by two reviewers using the checklist. We used regression analysis to assess the association between completeness of reporting (measured as the number of items in the CONSORT extension checklist for reporting of abstracts in pilot trials contained in each abstract) and factors influencing the quality of the reports.

Results: Two hundred and twenty-eight (228) articles were retrieved, of which 92 met the inclusion criteria. The mean CONSORT extension score was 8.3/16 (standard deviation 1.7); the least reported items were the source of funding (1% [1/92]), trial registration (13% [12/92]), randomization sequence (13% [12/92]), number randomized to each arm (16% [15/92]), and number analyzed in each arm (16% [15/92]). Multivariable regression analysis showed that pharmacological intervention pilot trials [incidence rate ratio (IRR) = 0.88; 95% confidence interval (CI), 0.81–0.97] were significantly associated with better reporting. Other factors such as structured abstract (IRR = 1.10; 95% CI, 0.99–1.23) and CONSORT endorsement (IRR = 1.10; 95% CI, 0.99–1.23) only showed minimal relationship with better reporting quality.

Conclusion: The quality of reporting of abstracts of heart failure pilot trials was suboptimal. Pharmacological intervention was significantly associated with better reporting. These findings are consistent with previous research on reporting of trials.

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Background

Numerous challenges confront readers while accessing the literature; these include but are not limited to the enormous volume of published work, the high cost of obtaining articles especially in resource-limited settings [1], and language constraints when articles are not writ- ten in users' language [2]. The outcome of this has been an over-reliance on abstracts for articles as a one-stop point for most researchers. Abstracts of journal articles o r scientific papers often provide readers with an over- view of the content of the full article. As a result, researchers tend to rely on abstracts as a concise source of information [3] and in making decisions on which publications to read in detail [4]. Furthermore, researchers rely largely on the abstract when deciding whether to include an article in a systematic review [5]. All these factors make the abstract a key section of the scientific publication. It is, therefore, important that abstracts of articles are consistent with what is reported in the text and capture essential information.

Randomized control trials (RCT) constitute a significant portion of clinical studies and most times are the core component for systematic reviews. However, the quality of reporting of RCTs have over the years attracted many questions, mostly related to consistency and completeness of reports [6]. The Consolidated Standard for Reporting of Trials (CONSORT) checklist was conceptualized in 1996 to address these issues. Its publication and instant acceptance led to revisions in 2007 and 2010 [7, 8]. Many journals have adopted the CONSORT checklist, and it has been shown to improve the quality of reporting RCTs [9–11].

The overwhelming acceptance of CONSORT checklist has led to the development of extensions to incorporate other types of RCTs. Due to the need to widen the scope of the checklist, in 2016, the CONSORT extension checklist for abstracts of pilot trials was developed to aid adequate reporting of pilot trials [12], an important but often neglected arm of medical research [13].

We conducted this systematic survey to evaluate the quality of reporting of abstracts of pilot RCTs in heart failure published 1990–2016. Heart failure, defined as a clinical condition in which the heart does not pump blood sufficiently or does so at a higher pressure to maintain the body's need [14, 15], has been a prominent cause of cardiovascular disease burden in Africa in the last two decades [16, 17]. It has also attracted many clinical trials in the last two decades (1990–2016), most of which were preceded by pilot trials [17]. The quality reporting is defined as complete reporting of the 16 items in the CONSORT extension checklist.

The aims of this survey are to (1) evaluate the quality of reporting of abstracts of pilot RCTs in the past 26 years (1990–2016), using the CONSORT extension for reporting of abstracts of pilot trials; (2) identify aspects of the checklist that are consistently reported;
(3) identify factors associated with better reporting of abstracts; and (4) determine the quality (completeness) of abstracts of pilot trials.

Methods

Randomized controlled pilot trials in heart failure published from 1 January 1990 to 30 November 2016 were searched for in line with the systematic survey method as previously described [17]. Abstracts were selected if they were de- scribed as random, randomly allocated, and randomized. We searched the MEDLINE (PubMed), Cochrane Con- trolled Trials Register, Scopus, and African-wide information databases (search strategy in the Additional file 1). We limited our search to pilot trial reports written in English language only. Two reviewers independently screened the identified papers and those finally selected to assess the quality of reporting of abstracts using the 16 items of CONSORT extension for reporting of abstract of pilot trials. We assigned a score of one to an item on the CONSORT checklist if the item was reported in the abstract. The overall quality of abstract was calculated as the proportion of "yes" responses. We classified abstracts that re- ported all the 16 items in the CONSORT checklist as adequate quality reporting.

We hypothesized that pilot trials published in high impact journals [18], published in CONSORT-endorsing journals [19, 20], those on pharmacological interventions [20], studies with large sample sizes [21], and industry-funded studies [22] would have better reporting quality.

The protocol for this systematic survey [17] was registered with PROSPERO (CRD42016049911) and written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Protocols (PRISMA-P) [23].

Statistical analysis

The analysis was with IBM statistical package for social sciences (IBM SPSS) version 24 (IBM Corp., Armonk, NY) and STATA 9.0 (College Station, TX). We calculated the percentage of trials that scored yes on each of the 16 items and the associated 95% confidence interval (CI).

We reported categorical variables as count and percentages; continuous variables are summarized as mean (standard deviation (SD)) or median (interquartile range (IQR)). Incidence risk ratio (IRR) was calculated to identify factors associated with better reporting. Negative binomial regression was conducted to determine factors associated with better reporting quality.

Results

Our search identified 228 articles; after the screening one hundred and thirty-six articles were found to be

ineligible based on several reasons (Fig. 1). A total of 92 articles from 48 journals were eligible; among these, 12 were conference presentations. The three highest contributing journals were *European Journal of Heart Failure* (9 articles; 9.8%), *American Heart Journal* (8 articles; (8.7%), *Journal of American College of Cardiology* (7 articles; 7.6%), and *Journal of Cardiac Failure* (7 articles; 7.6%).

Study characteristics

The estimate of Kappa statistic for inter-rater agreement for screening publications for eligibility was 0.82 [95% confidence interval (CI), 0.76−0.87]. A majority (71%) of the studies were published between 2001 and 2016 (Table 1). Both pharmacological intervention studies and non-pharmacological intervention studies were 45 (49%), respectively; two studies (2%) had both pharmacological and non-pharmacological interventions. The abstract presentation was structured in 80% of the studies. In 62 of 92 (67%) of the studies, the CONSORT statement was not endorsed by the publisher. Most (74%) of the studies were conducted at a single site.

Quality of reporting of abstracts of pilot trials

None of the studies reported all the 16 items in the check- list (Table 2), the maximum reported number of items was 12, with a mean (SD) of 8.3 (1.7) items. The most reported item was the type of intervention intended for each group

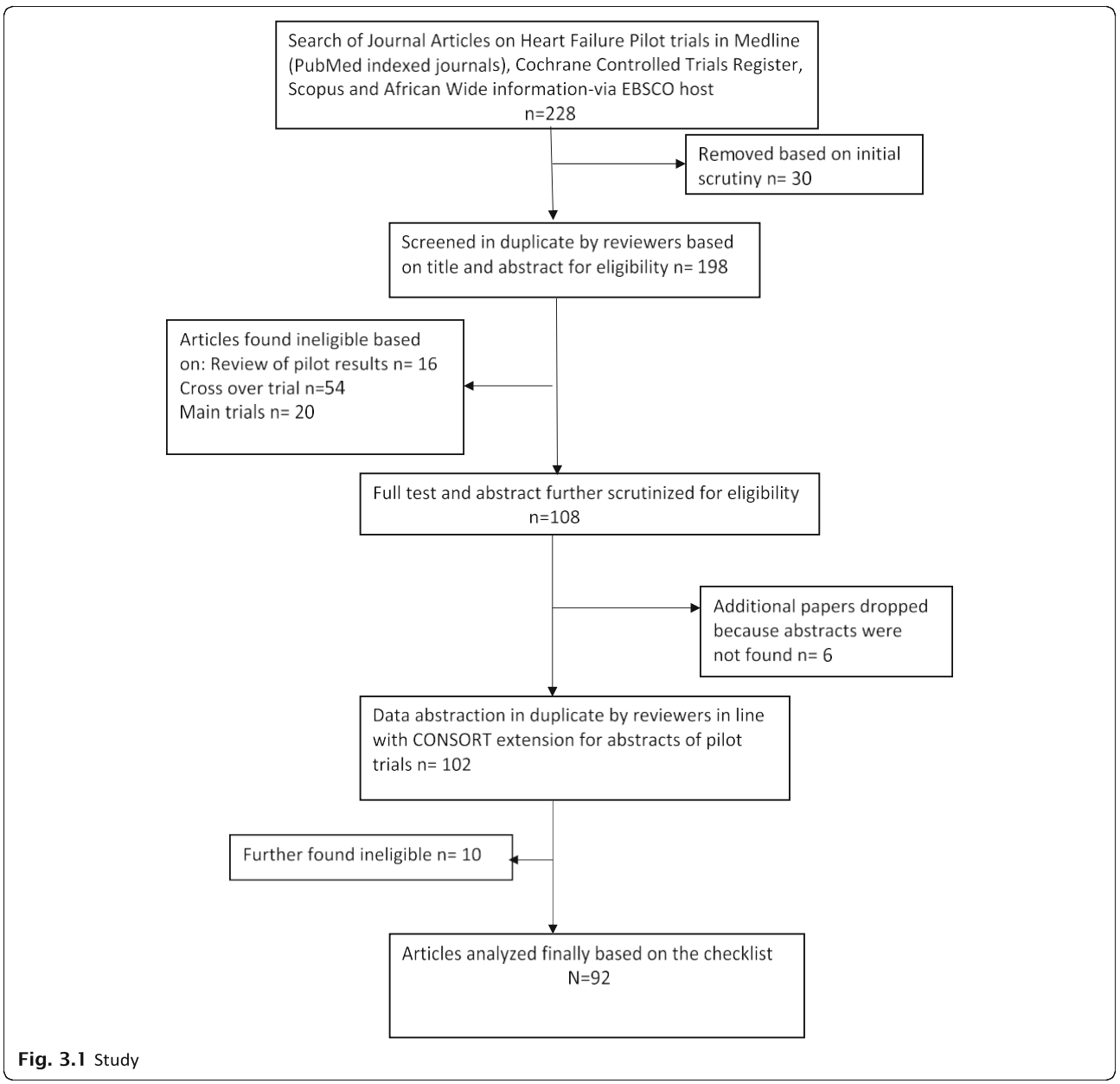

Fig. 3.1 Study

Table 3.1 Characteristics of included papers: *n* = 92

Characteristic	Count (%)/median (Q1; Q3)
Year of publication	
1990–2006	26 (28%)
2007–2016	66 (72%)
Intervention type (*n* = 90)	
Pharmacological	45 (49%)
Non-pharmacological	45 (49%)
Both pharmacological and non-pharmacological	2 (2%)
Abstract format	
• Structured	74/92 (80%)
• Unstructured	18/92 (20%)
CONSORT endorsement	
• Yes	30/92 (33%)
• No	62/92 (67%)
Number of sites	
• Single	61/82 (74%)
• Multiple	21/82 (26%)
Study duration in months (*n* = 68)	3.0 (2.6; 6.1)
Sample size (*n* = 88)	41 (24; 88)

CONSORT Consolidated Standards of Reporting Trials, *Q1* first quartile, *Q3* third quartile

99% (95% CI 91; 99), followed by specified objectives of the pilot trial 94% (95% CI 89; 99) and pre-specified outcome to address pilot trial objectives 97% (95% CI 90; 98).
The least reported item was funding source 1% (95% CI 0.16; 6.9); however, 21 of 92 (22.8%) studies re- ported funding source in the main manuscript but not in the abstract. Inadequately reported items include the randomization method used 13% (95% CI 8; 19), trial registration information 13% (95% CI 7; 21), and the number of

participants screened in each arm 16% (95% CI 9; 26). Recruitment status, an item in the CONSORT checklist that addresses conference presentation, was low with 2%

(95% CI 5; 8) among the 12 conference abstracts.
Multivariable analysis (Table 3) of factors associated with reporting quality showed pharmacological intervention is significantly associated with better reporting quality (IRR 0.88; 95% CI 0.81; 0.97; *p* value 0.01), while
structured abstract (IRR 1.10; 95% CI 0.99; 1.23; *p* value 0.5) did not have a strong association. Journals which endorsed CONSORT was not a significant factor (IRR 1.10; 95% CI 0.99; 1.23; *p* value 0.06).

Discussion and conclusions

The CONSORT extension for reporting of abstracts of pilot trials was introduced in 2016 to standardize the reporting of abstracts of such studies. We undertook this

Table 3.2 Publication adherence to CONSORT checklist for abstract of pilot trials *n* = 92

	Item	Criteria	Count	Percent (95% CI)
Title	Identifier	Title identifies the study is a randomized controlled pilot trial	65	71 (60; 79)
Description	Trial design	Description of pilot trial design (e.g., parallel or cluster)	30	33 (23; 44)
Method	Eligibility	Eligibility criteria for each participant	81	88 (78; 94)
	Settings	Setting where pilot was conducted	29	32 (22; 47)
	Interventions	Interventions intended for each group	91	99 (91; 99)
	Objectives	Specific objectives of the pilot trial	89	94 (89; 99)
	Outcomes	Pre-specified assessment or measurement to address the pilot trial objectives	89	97 (90; 98)
	Randomization sequence generation	Describe how participants were allocated to the interventions	12	13 (8; 19)
	Blinding (masking)	Whether or not participants, caregivers, and those assessing the outcomes were blinded to group assignment	20	22 (15; 31)
Results	Number randomized	Number of participants screened	15	16 (9; 26)
		Number randomized to each group for the pilot objectives	41	45 (36; 53)
	Recruitment	Trial status (for conference abstracts)	2	2 (5; 8)
	Numbers analyzed	Number of participants analyzed in each group of pilot objectives	15	16 (11; 24)
	Harm	Important adverse events or side effects	28	30 (23; 39)
Conclusion	Result interpretation	General interpretation of results of pilot trial	80	87(76; 93)
	Plans	Any implication for future trial	20	22 (15; 30)
Registration	Trial registration	Registration number of trials	12	13 (7; 21)
	Funding	Source of funding	1	1 (0.16; 6.9)

CI confidence interval

Table 3.3 Univariate and multivariable analysis of factors associated with reported items

Item	Univariate		Multivariable	
	IRR (95% CI)	*p* value	IRR (95% CI)	*p* value
Year of publication				
• 1990–2006 • 2007–2016	0.99 (0.91; 1.08)	0.86 (0.91; 1.13)	1.07	0.74
Intervention type				
• Pharmacological • Non-pharmacological	0.93 (0.86; 1.01);	0.07 (0.81; 0.97)	0.88	0.01
Abstract format				
• Structured • Unstructured	1.11 (0.99; 1.24)	0.08 (0.99; 1.23)	1.10	0.05
CONSORT endorsement				
• Yes • No	1.07 (0.98; 1.16)	0.12 (0.99; 1.23)	1.10	0.06
Number of sites				
• Single • Multiple	1.08 (0.97; 1.22)	0.14 (0.92; 1.15)	1.02	0.62
Study duration*	1.03 (1.01; 1.06)	0.02		
Sample size*	1.01 (0.96; 1.07)	0.63		

IRR incidence rate ratio, *CI* confidence interval
*Incident rate for change in 1 unit on the log scale

survey to gauge the current practice using heart failure pilot trials as a sample to track reporting quality improvement expected with introduction and adherence to the extension. We found inadequate reporting quality in keeping with previous articles evaluating adherence to CONSORT checklist on abstracts [8, 24, 25].

The least reported item was the funding source like findings in a previous study [26]. The full declaration of funding source in a publication can give the reader the opportunity to make their own assessment regarding potential conflict of interest. However, we noticed that 22/96 may not be unrelated to word count stipulation by individual journals. Often, this poses a challenge to authors on what to include in abstracts, and there may be the need for CONSORT extension checklist developers to consider this limitation.

The randomization sequence was also poorly re- ported. It is an item that can provide acceptable comparability between groups if properly reported. Some previous studies have commented on this methodological flaw [10, 27–29], explaining that this could be because of attachment of more relevance to clinical than the methodological aspect of RCTs. There has been corroborating evidence in other studies supporting a correlation between deficient reporting and poor trial methodology [30–32].

Many of the articles were also silent on the blinding, and when used, some failed to state the group blinded in the studies. Not being explicit about blinding erodes the integrity and internal validity of the reports, and it is a potential source of bias among the readers [33, 34].

Reporting on harm was low at 28%; this is an essential item as it informs the design and applicability of intended larger trials. Previously, this safety reporting has often been inadequate or neglected [35]. And, in literature, there is highly variable adherence to reporting of harm [36, 37].

Methodological aspects reported include intervention type, specific objective, and outcomes to be assessed. Many of the articles identified them as pilot trials; this was despite the constraint of word limit by journals, a reason often adduced as responsible for not including this [10, 26, 29]. Also, pilot trials with pharmacological intervention, those with structured abstracts, and those published in the journal that endorses CONSORT were more likely to report on the items on the checklist. The last point brings to fore why it is important for journals to have stipulated reporting format to ensure that the quality of abstracts' report is improved.

of the articles had information on funding in other places rather than the abstract, and this our study is limited in scope by using only articles published in the English language. We also used a recently produced checklist to evaluate publications done by authors who at the time of writing of the articles probably had no reporting checklist to follow.

In conclusion, the reporting quality of abstracts of heart failure trial measured by the number of items reported was suboptimal; the need to guard against this was the reason that informed the introduction of CON- SORT extension checklist. The desire is that increasingly journals will demand adherence to the checklist by authors. Ultimately, we hope that there will be a marked improvement in the quality of report of abstracts in the coming years.

Additional file

Additional file 1: Database search strategies. (DOCX 21 kb)

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Availability of data and materials
The data and materials are available on request from the authors.

Authors' contributions
GI, LT, BM, MZ, and MC made a substantial contribution to the conceptualization and design, acquisition of data, analysis, and interpretation. GC, LT, and BM have been involved in drafting the manuscript and revising the content for important intellectual content. BM, LT, GC, MC, and MZ gave the final approval of the version to be published. LT, BM, GC, MZ, and MC agreed to be accountable for all aspects of the work in ensuring accuracy and intellectual content.

Ethics approval and consent to participate
The study did not involve any human subjects, so ethics approval or consent was not required.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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CHAPTER FOUR
The impact of pericardiocentesis on the effectiveness of adjuvant corticosteroids in Tuberculous Pericarditis: An IMPI-1 Trial Subgroup Analysis

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"On behalf of the IMPI-1 Investigators"

Keywords: Pericardiocentesis, Prednisolone, Pericarditis, subgroup analysis

Abstract

Background

Corticosteroids, by dampening the immune response to tuberculous antigens within the pericardium may reduce the size of the inflammatory effusion and reduce major adverse pericarditis related outcomes in those with effusive TB pericarditis who are unstable. However, in the first investigation of the management of pericarditis trial (IMPI-1) adjunctive corticosteroids had a neutral effect on the composite outcome of death, recurrent tamponade requiring pericardiocentesis and constrictive pericarditis. In the trial, a large proportion of the randomised study cohort underwent pericardiocentesis at the discretion of the responsible clinician, as part of their initial management. By evacuating the pericardium of compressive pericardial fluid, pericardiocentesis may have an impact on the subsequent incidence rate of constrictive pericarditis, recurrent tamponade and death. Whether the procedure modified the effectiveness of adjunctive steroids in the trial is not known.

Objective: Our aim in this subgroup analysis is to explore whether performing pericardiocentesis modified the effects of prednisolone among patients with effusive TB pericarditis.

Hypothesis: We hypothesised that among patients with tuberculous pericarditis, the effects of prednisolone would be similar among those who received pericardiocentesis at baseline and those who did not (because it was not indicated).

Method

Outcomes: The primary efficacy outcome was the composite of death, constrictive pericarditis or cardiac tamponade requiring pericardiocentesis. Secondary outcomes include death, constrictive pericarditis, cardiac tamponade requiring pericardiocentesis, constriction or cardiac tamponade, and hospitalisation.

Analysis: The subgroup analysis was performed by adding an interaction term between pericardiocentesis (yes vs no) and treatment group (prednisolone vs placebo) to the main effects model using the Cox proportional-hazard model for all outcomes. We used forest plots to report the effect estimate as a hazard ratio (95% confidence interval) for each subgroup and a p-value for the test of interaction. The criterion for statistical significance was set at alpha = 0.05, and this was not adjusted for multiple testing since these analyses are exploratory.

Results

Two-thirds of the study population presented with large pericardial effusion, and 60.5% (847/1400) had pericardiocentesis at physician discretion. There was no statistically significant reduction in composite outcome with pericardiocentesis (p-value for the interaction with prednisolone was 0.71). Effects on the secondary outcomes were similar in both groups with no significant risk reduction.

Conclusion

Among participants presenting with tuberculous pericarditis, the effect of adjunctive steroid on the primary efficacy outcomes of death, constrictive pericarditis and cardiac tamponade requiring pericardiocentesis were similar among those who received pericardiocentesis procedure at baseline because it was indicated and those who did not receive it. This finding would need to be confirmed in future non-inferiority trials.

4.1 Introduction

A comprehensive summary of the background, rationale, trial design, research questions addressed, results and conclusion of the IMPI-1 trial is provided in chapter one. In the trial, patients who were randomised to receive adjuvant corticosteroids did not experience a reduction in the composite outcome of death, constrictive pericarditis and pericardial tamponade requiring pericardiocentesis at the prespecified time of six months compared to those randomised to receive standard therapy. Corticosteroids, by dampening the immune response to tuberculous antigens within the pericardium may reduce the size of the inflammatory, exudative pericardial effusion and therefore reduce major adverse pericarditis related outcomes in those with effusive TB pericarditis who are unstable. Approximately 60% of the trial participants in both arms underwent pericardiocentesis before randomisation. The decision to undergo pericardiocentesis was left to the discretion of the treating physician but was encouraged where there were clinical or echo features of significant cardiac compression.

There is a reason to suspect that the outcome of the study may have been influenced by the high proportion of participants who underwent pericardiocentesis, precisely because it is possible that pericardiocentesis may have modified the potential impact of corticosteroids on the composite outcome. There are theoretical reasons to believe that patients with large inflammatory, exudative effusions are at higher risk of major adverse events and that evacuation of the fluid alone may alter the natural history of the condition and, therefore, the response to steroids.

Pericardiocentesis is a life-saving procedure following cardiac tamponade as it reduces the raised intrapericardial pressure leading to lower intracardiac pressure; thereby improving patient's outcome and ultimately a reduction in mortality (Krikorian and Hancock 1978; Kopecky et al. 1986b; Callahan, Seward, Nishimura, Miller Jr, et al. 1985). Pericardiocentesis followed by use of anti-tuberculosis medication leads to favourable results irrespective of HIV status of patients (Reuter, Burgess, Louw, et al. 2006). Intermittent drainage and early initiation of anti-tuberculosis therapy are associated with a low risk of constriction and death (Reuter et al. 2007).

The presence of fluid in the pericardial space is proinflammatory, and fluid accumulation develops as an inflammatory response to tuberculoproteins (Fowler 1991). The bacillary load is a determinant of the adverse event in pericardial effusion (Pasipanodya et al. 2015b) and reduction of the fluid through pericardiocentesis can reduce the bacillary load and thus lead to a reduction in the rate of constriction and theoretically reduce the rate of major adverse events. However, the influence of pericardiocentesis on long-term complications such as constrictive pericarditis is not apparent. For example, in effusive-constrictive pericarditis, pericardiocentesis relieves the pericardial tamponade and aids in making the diagnosis by finding the persistent elevation of right atrial end-diastolic pressure and interventricular end diastolic pressure after reduction of intrapericardial pressure. However, the removal of the fluid does not prevent subsequent development of constrictive pericarditis or need for pericardiectomy later (Hancock 2004; Kolek 2011).

Observational studies in patients who had 80-100mls of pericardial fluid aspirated before high dose oral prednisolone and anti-tuberculosis medication administration showed good outcome (Strang et al. 1987). Following open surgical drainage and use of prednisolone in 240 patients with TBP, a good outcome was shown with the anti-tuberculosis regimen, and it was neither dependent on the administration of prednisolone nor drainage. In the study, open drainage at admission had no effect on pericarditis related death or need for pericardiectomy following administration of corticosteroids (Strang, Gibson, et al. 1988).

While there is evidence that pericardiocentesis relieves immediate tamponade, there have been no randomised controlled studies to test the impact of pericardiocentesis on re-accumulation of pericardial fluid and recurrence of tamponade, constrictive pericarditis and death. In a 10-year follow-up of 383 patients who were randomised to prednisolone compared to placebo in addition to anti-tuberculous therapy; corticosteroids reduced adverse events of death from pericarditis, pericardiectomy, the need for repeat pericardiocentesis and subsequent open drainage. In the subgroup analyses, of these relatively small studies, the outcome following use of prednisolone was better in those who had drainage than those who did not (Strang et al. 2004). Furthermore,

for every adverse event, there was treatment interaction between open drainage and prednisolone (11% in prednisolone and drainage, 19% in prednisolone and no drainage). Also, prednisolone conferred a significant survival advantage compared to placebo after adjusting for age and sex (HR 0.64; 95% C. I 0.41-0.99).

A systematic review of corticosteroid uses in all forms of tuberculosis included six trials focusing on pericarditis and reported that there was a significant principal reduction in mortality of 17% (RR 0.83; 95% C. I 0.74-0.92) (Critchley et al. 2013).

Cellular immunity plays a significant role in TBP, as shown by the enhanced type1 T-helper cells (TH-1) response, leading to high interferon gamma which suppresses type 2 T-helper cells (TH-2) responses. There is also a lower level of interleukin 10 (IL-10) compared to the level in bacterial effusion, due to the suppression effect of IL-10 on TH-I (Burgess et al. 2002). Therefore, use of prednisolone may attenuate the inflammatory response leading to the better outcome; however, pericardiocentesis will lead to the removal of the profibrotic and proinflammatory modulators, raising a question on whether the use of steroids will still have the same effect following pericardiocentesis. Conclusive research has not provided this answer as it is not certain whether the effects of steroids work better in patients with large tuberculous pericardial effusions compare to patients with small pericardial effusions.

To address the possibility that the impact of adjuvant corticosteroids compared to placebo may have been modified by pre-randomization pericardiocentesis we performed a subgroup analysis of the IMPI-I trial.

4.1.1 Hypothesis

The specific hypothesis to be tested was; among participants presenting with large pericardial effusions, the effect of adjunctive steroids on the composite outcome of death, pericardial tamponade requiring pericardiocentesis and constrictive pericarditis corticosteroids will be similar irrespective of pericardiocentesis status at baseline. The rationale for the study

hypothesis is based on the premise that because patient selection for pericardiocentesis by the Physician in the IMPI-1 trial, was on individual indications (this may have selected out the patients who were most likely to develop the composite endpoint and benefit from adjuvant corticosteroids). This is as opposed to a protocol that mandated either routine pericardiocentesis for all patients or no pericardiocentesis for all patients (not feasible or ethical) presenting with pericardial effusion (Kilpatrick and Chapman 1965b; Sagrista-Sauleda, Merce, and Soler-Soler 2011).

4.1.2 Aims and Objective

The main aim of this subgroup analysis was to determine if pericardiocentesis at baseline modified the impact of adjuvant corticosteroid therapy on the composite outcome of death, constrictive pericarditis and recurrent pericardial tamponade in patients with large tuberculous pericardial effusions.

Further objectives were to determine if pericardiocentesis at baseline modified the impact of adjuvant corticosteroids on each component of the composite outcome in the same patients.

4.2. Methods

The IMPI-1 trial enrolled 1400 patients with either definite or probable tuberculous pericarditis to participate in the trial from 19 hospitals in 8 African countries, from January 2009 to February 2014. The patients were randomised to six weeks of 120mg prednisolone and five doses of intradermal *Mycobacterium* indicus pranii over three months as compared with placebo. The median follow-up period was 636.5 days (IQR, 317.5 to1085.5). In this predefined subgroup analysis, patients in both treatment arms (prednisolone versus placebo) were divided into two groups (Figure 4.1), depending on their baseline pericardiocentesis status (performed versus not performed). The primary efficacy outcome (composite of death, cardiac tamponade requiring pericardiocentesis and constrictive pericarditis) was compared for each group using a Cox

proportional-hazard model with an interaction term for treatment effect across the subgroup. The point effect estimate was reported as hazard ratio with 95% confidence interval and presented with a forest plot. The analysis was exploratory, so the P-value was not adjusted for multiple testing. Continuous variables are represented as median with interquartile range unless otherwise specified; nominal variables are presented as counts (%). Cox proportional hazard model for the outcome was used to add an interaction term between pericardiocentesis (performed and not performed) and the treatment group (prednisolone and placebo) to the primary effect model. The effect estimate for each subgroup was reported as Hazard ratio at 95% confidence interval and presented with a forest plot. Level of significance was determined using p-value for test of interaction with alpha value=0.05. The p-value test for interaction described whether a history of performing pericardiocentesis at baseline or not interacts with the overall treatment effect of prednisolone on the primary efficacy outcome. The analysis was performed using STATA 14 (StataCorp. 2013. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

4.3. RESULTS

4.3.1 Study Population Characteristics

The prednisolone arm had 706 participants and the placebo arm 694, with a median follow-up of 635 days (Figure 4.1). Sixty-seven per cent (933/1400) of the study population were females, 48% presented in NYHA stage III and IV, 67% were HIV positive, and 67.3% had CD4 cell count less than 200.

Eight hundred and forty-seven (847) of the study population (60.5%) underwent pericardiocentesis. There was no difference in age, sex and weight between the groups. Of the 847, approximately half (428, [50.7%]), received prednisolone, while 416 (49.5%) received placebo. Of the 553 patients who did not undergo pericardiocentesis 278 (50.2%) were randomised to receive prednisolone. Table 4.I provides the differences in baseline

characteristics stratified by pericardiocentesis status and whether they were in the active or placebo arms. Overall a more significant proportion of patients who received pericardiocentesis had a heart rate higher than 100, compared to those who did not ((60.5% vs 46.9%). Similarly, the proportion of participants who underwent pericardiocentesis with systolic blood pressure less than 90, was almost double the proportion ((9.9 vs 4.2%) who did not undergo pericardiocentesis. Furthermore, a much larger proportion of the group that underwent pericardiocentesis had large effusions (85.7% versus 39.9%) and had NYHA Class III and IV heart failure symptoms compared to those who did not undergo the procedure (43.8% versus 40%). Also, a slightly higher proportion in the performed group tested positive for HIV (68.6% versus 64.9%) and had a higher CD4 cell count, compared to the other group (39.6% versus 37.2%). At presentation, the proportion of participants in the performed group who were on anti-tuberculosis medications was more than in the not performed group - 96.2% versus 94.9% (Table 4.1).

4.3.2 Impact of Corticosteroids by pericardiocentesis at baseline

The outcome status was known in 1371/1400 participants at the end of the trial. The primary composite outcome occurred in 25% (107/428) of those that had pericardiocentesis and 14.6% (61/419) of the participants who did not have pericardiocentesis; secondary outcomes were recorded in 28.3% (121/428) following pericardiocentesis and 17.9% (75/419) without pericardiocentesis.

Compared to those patients who did not undergo pericardiocentesis at baseline, those participants who underwent pericardiocentesis had a non-significant risk reduction of 7% for the primary outcome (HR 0.93, 95% C.I 0.71-1.2, p-value for interaction 0.709). Those who underwent pericardiocentesis had 18% risk reduction in tamponade (HR 0.82, 95% C. I 0.45-1.43, p-value for interaction 0.583), 47% risk reduction in constriction (HR 0.53, 95% C.I 0.30-0.93, p-value for interaction 0.759) and 12% increase in the risk of death over the follow-up

period (HR 1.12, 95% C. I 0.82-1.54, p-value for interaction 0.776). However, none of these effects in the secondary outcome was statistically significant.

4.4. DISCUSSION

The main findings from this subgroup analysis include that: a] amongst patients in the IMPI trial, the use of pericardiocentesis as part of the initial management strategy did not modify the neutral impact of adjuvant corticosteroids on the composite outcome of death, recurrent tamponade needing pericardiocentesis or constrictive pericarditis compared to placebo. Pericardiocentesis did not modify the impact on of corticosteroids on the secondary individual outcomes of death, tamponade and constrictive pericarditis at six months compared to placebo; and c] pericardiocentesis may be a marker for sicker more hemodynamically compromised patients at baseline and worse outcomes at six months.

In this subgroup analysis, the baseline clinical characteristics show that more participants who underwent pericardiocentesis at baseline had tachycardia, systolic blood pressure lower than 90mmHg, NYHA functional class III and IV, and presented with a larger size of effusion. The group, therefore, had more likelihood of presenting in cardiac tamponade and it is not surprising that the clinical condition influenced the managing physician's decision for pericardiocentesis (a life-saving intervention for patients who present with cardiac tamponade) for patients in this group. Removal of even a minimal amount of fluid in emergencies can improve the survival of patients who present in cardiac tamponade.

Observational evidence on the impact of the evacuation of the pericardium in patients with large tuberculous effusion who were randomised to receive steroids or placebo is not clear (Strang et al. 1987). However, in this analysis pericardiocentesis at baseline did not have any significant modification of the effect of adjunctive steroid on the study outcomes and is in keeping with our hypothesis. It is possible that amongst patients presenting with larger effusions and more evidence of significant cardiac compression; corticosteroids may have led to improved

outcomes compared to placebo in the absence of pericardiocentesis because of its effect in halting the immune response within the pericardium and reducing the amount of inflammatory exudates. However, by performing the pericardiocentesis and removing the target of the steroids, the two patient groups (pericardiocentesis and no pericardiocentesis) were rendered almost equal regarding the effectiveness of adjunctive steroids.

Tuberculous pericarditis is paucibacillary and large pericardial fluid accumulation is said to be an inflammatory response to tuberculo-proteins (Fowler 1991); tuberculous pericardial effusion is proinflammatory, an assertion that has been scientifically proven by the establishment of the role of cellular immunity pathogenesis of TBP. Evidence for this is the finding of raised interferon gamma in TBP due to TH-I response leading to suppression of TH-2 response, and reduction in IL-10 compared to the level in bacteria effusion as the later suppresses TH-1(Burgess et al. 2002). Another study also reported on the elaboration of such inflammatory markers such as interleukin 10 and interferon gamma in the pericardial fluid of patients with pericardial effusion (Ntsekhe et al. 2013b). The implication of this could be that if the cause of the inflammation is adequately addressed by pericardiocentesis, the impact of corticosteroids may not have any influence on the long-term outcome in patients.

Amongst patients who do not have tuberculous pericarditis the long term impact of pericardiocentesis and steroids are not known, In a study to evaluate if conventional pericardiocentesis should be carried out in patients who present with large pericardial effusion, the result among the 71 patients showed that pericardiocentesis did not play an essential role in the long-term outcome (Mercé et al. 1998). There was documentation of a previous pericardiocentesis in 80% of patients that had persistent effusion; 38 of the 40 patients offered conservative drainage had a resolution of effusion within weeks without intervention. However, higher than 98% of the patients had idiopathic pericarditis. The condition is benign with low rates of constrictive pericarditis recurrent pericarditis and death because none of these patients had tuberculous pericarditis or purulent pericarditis where the rates of constrictive pericarditis and recurrent tamponade are high. Therefore, these results may not apply to the understanding of

the role of pericardiocentesis the IMPI-1 results.

It is notable that pericardiocentesis in IMPI-1 did not prevent subsequent repeat accumulation of pericardial effusion requiring repeat pericardiocentesis as 4% of participants had re-accumulation with tamponade. Also, pericardiocentesis did not influence the outcome of constriction; 8% of the trial patients who had the pericardiocentesis progressed to constriction (Mayosi et al. 2014). However, in the trial, the overall rate of constrictive pericarditis and recurrent pericardial tamponade and death was low compared to historical studies where the rate of pericardiocentesis is low. In the IMPI Registry (Mayosi, Wiysonge, Ntsekhe, Volmink, Gumedze, Maartens, Aje, Thomas, Thomas, and Awotedu 2006) pericardiocentesis was undertaken in 37% of patients, and the rate of major adverse pericardial outcomes was between 32 and 44% depending on baseline variables (Mayosi et al. 2008b; Ntsekhe et al. 2008).

The subsequent progression of some patients to constrictive pericarditis despite pericardiocentesis could be explained by the fact that despite pericardiocentesis, significant amounts of fluid remained in the pericardial space, and as already explained, this fluid is proinflammatory and a stimulant of pericardial fibrosis. While the analysis suggests that pericardiocentesis did not modify the effectiveness of steroids, what is still unclear is whether adjuvant corticosteroids given to patients with compressive hemodynamic where pericardiocentesis is not available would be effective. Our analysis was not designed to answer this question, which is unlikely ever to be tested given the mortality and morbidity benefits of the procedure under those circumstances. (ESC guideline). A possible interpretation of the study is that following pericardiocentesis, profibrotic and inflammatory cytokines rich fluid are removed; and evacuating compressive pericardial fluid in unstable patients with large pericardial effusion, may mitigate the potential effectiveness of corticosteroids in unstable patients, rendering them as neutral as they are in patients who are stable and do not need pericardiocentesis.

Conclusion

In this subgroup analysis, pericardiocentesis performed at baseline had no significant interaction with the effectiveness of prednisolone on the primary composite outcome or the secondary outcomes. This is in keeping with our hypothesis that the removal of inflammatory profibrotic pericardial fluid from patients who are hemodynamically unstable and unwell, may have neutralized the impact of corticosteroids in the study. A non-inferiority trial may be necessary to evaluate this concept further; while addressing the inflammation by use of fibrinolysis - the focus of the second investigation of the management of pericarditis (IMPI-2) trial may provide additional answers to tackling the complications of tuberculous pericarditis. The findings of this study are important because they indicate that even though pericardiocentesis may identify a high-risk group for adverse outcomes, the impact of adjuvant corticosteroids did not differ by pericardiocentesis status.

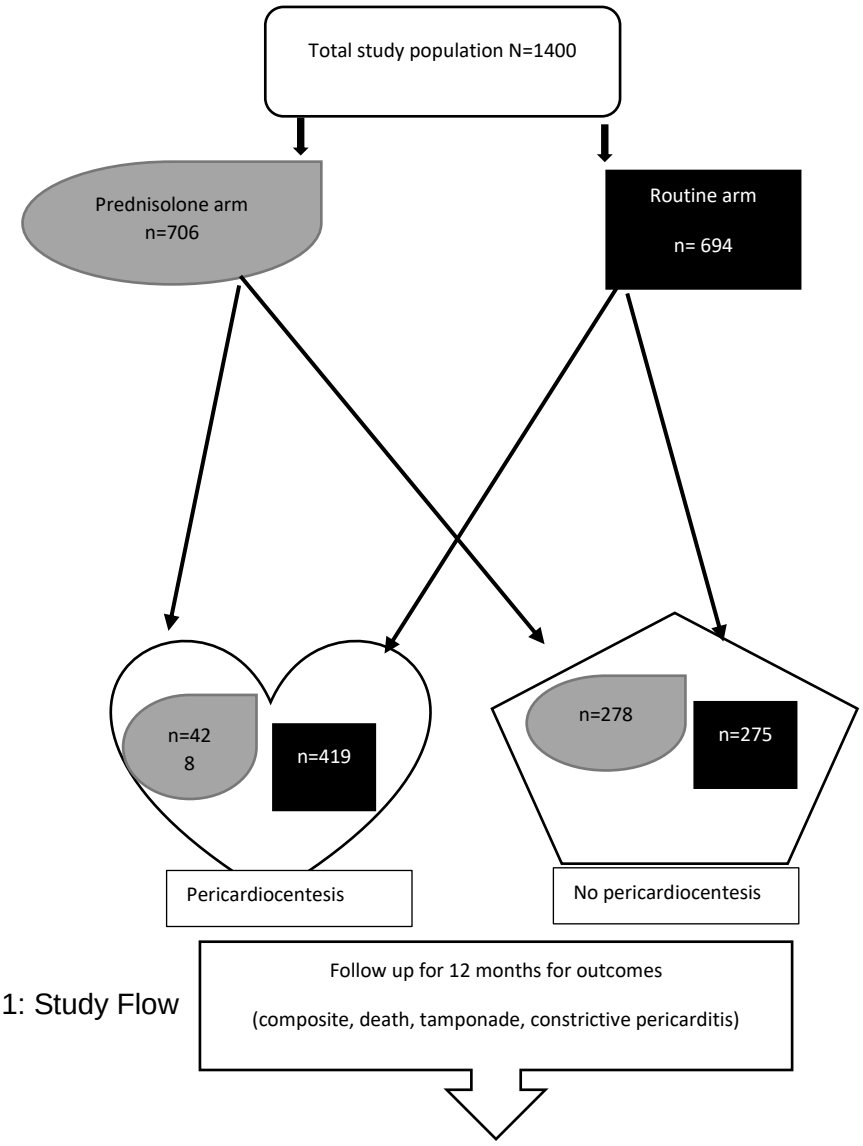

Figure 4.1: Study Flow

Table 4.1: Baseline Characteristics of the Subgroup[¶]					
Variable		**Pericardiocentesis n=847**		**No pericardiocentesis n= 553**	
	Overall N=1400	**Prednisolone n=428**	**Placebo n= 419**	**Prednisolone n=278**	**Placebo n=275**
Age – year	1400	34.9	35.3	37.2	35.7
Weight - Kg	1377	57.4	57.9	57.2	58.5
Female sex – no. (%)	616	192 (44.9)	172 (41.1)	125 (44.8)	127 (46.2)
Systolic BP - mmHg	1399	110	110	110	112
Diastolic BP -mmHg	1399	70	72	70	73
Systolic BP<= 90mmHg-no. (%)	106	45 (10.6)	38 (9.1)	14 (5.0)	9 (3.3)
Heart rate >100beates/min- no. (%)	680	167 (60.7)	253 (60.4)	132 (47.3)	128 (46.6)
Duration of symptoms- days	1400	30	21	30	30
NYHA Class[**] – no. (%)	1397				
I		71 (16.6)	60 (14.4)	66 (23.7)	59 (21.5)
II		169 (39.6)	183 (43.8)	173 (62.2)	169 (61.7)
III		132 (30.9)	127 (30.4)	31 (11.2)	40 (14.6)
IV		55 (12.9)	48 (11.5)	8 (2.88)	6 (2.2)
Size of effusion[**]- no. (%)	1359				
Small <1cm		14 (3.39)	10 (2.5)	36 (13.3)	46 (17.1)
Medium 1-2cm		45 (10.9)	50 (12.3)	127 (46.9)	109 (40.5)
Large >2cm		354 (85.7)	346 (85.2)	108 (39.9)	114 (42.4)
HIV Status- no. (%)	1400				
Positive		293 (68.6)	274 (65.4)	181 (64.9)	191 (69.5)
Negative		125 (29.3)	135 (32.2)	93 (33.3)	78 (28.4)
Unknown		9 (2.1)	10 (2.4)	5 (1.8)	6 (2.2)
Anti-tuberculosis medication at randomization[**]- no. (%)	1083	202 (96.2)	318 (96.9)	320 (94.9)	185 (96.9)
Antiretroviral medications at randomization[**]- no. (%)	927	50 (11.7)	48 (11.5)	49 (11.6)	56 (20.4)
CD4 cell count>200 cells/mm^3- no. (%)	776	106 (39.6)	96 (40.0)	51 (37.2)	60 (45.8)
Haemoglobin>10g/Dl -no. (%)	1393	188 (44.2)		131 (46.9)	
White blood cell count>10×10^9/L- no. (%)	1396	27 (6.35)	41 (9.8)	15 (5.38)	16 (5.8)

[¶] Median values are reported for continuous variables due to the presence of extreme values in some. No significant differences were seen on the baseline characteristics except for those with ** with p<0.005. HIV- Human immunodeficiency virus

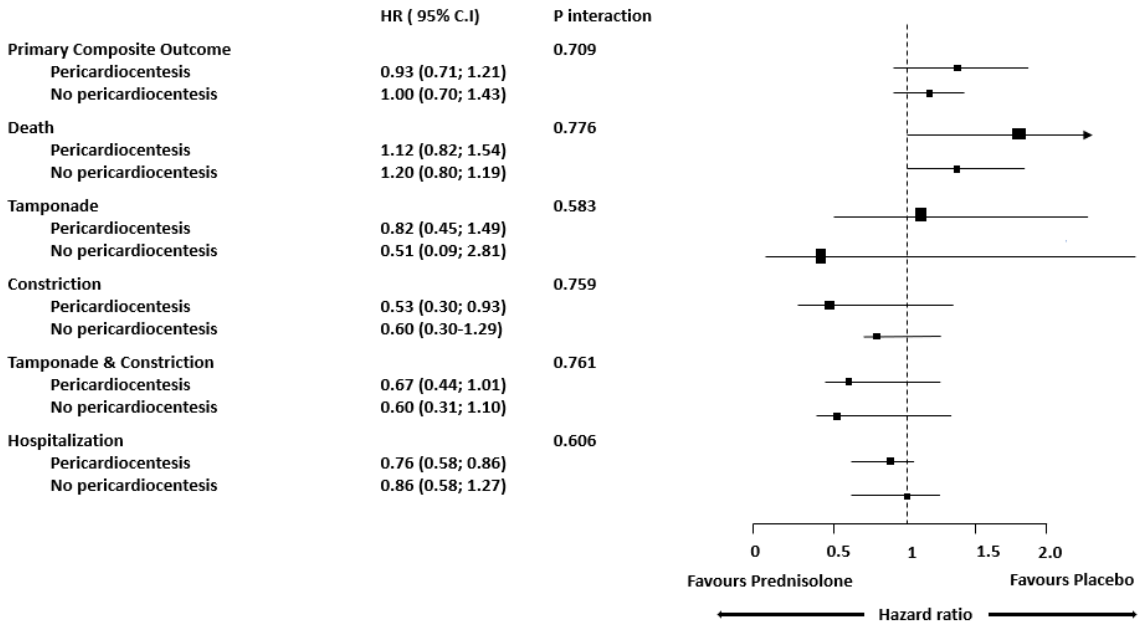

Figure 4.2: Forest plot of modification effect of prednisolone of primary efficacy outcomes by pericardiocentesis status at baseline

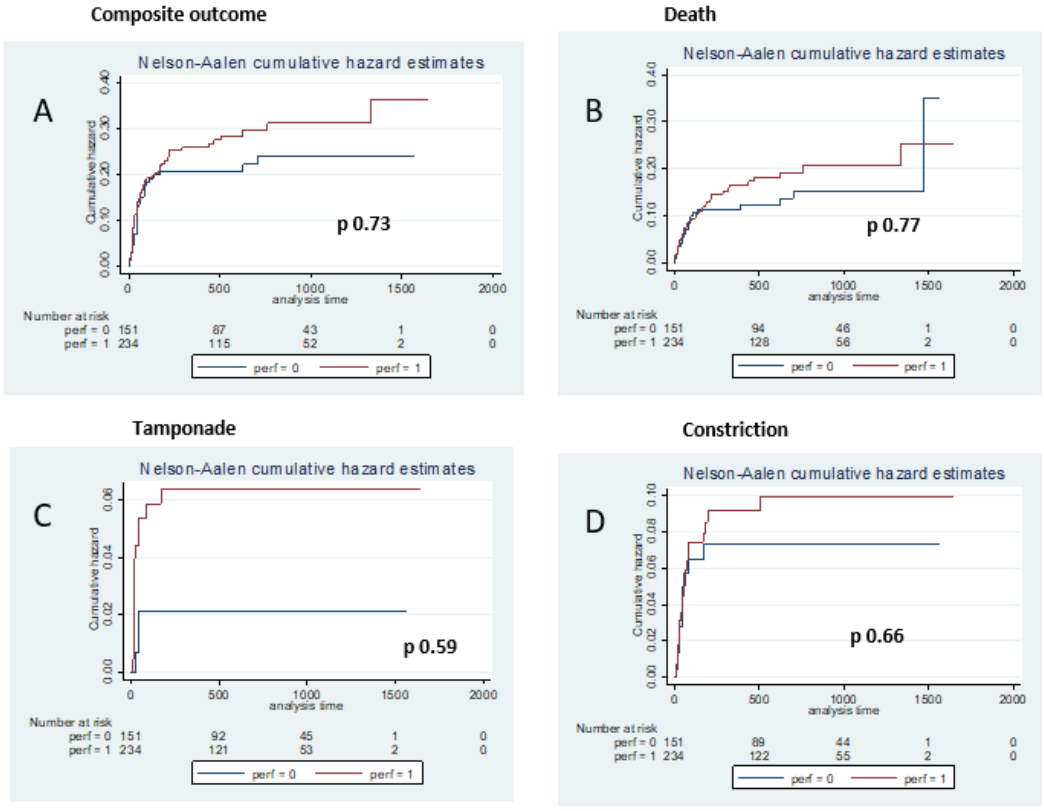

Figure 4.3: The cumulative hazard curves for pericardiocentesis on Primary and secondary outcomes

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CHAPTER FIVE

Preliminary Report of The Investigation for Management of Pericarditis (IMPI)-2: A two-phase trial with a dose-finding phase followed by a pilot randomised control trial of intrapericardial alteplase versus usual care for complete percutaneous pericardial drainage among patients with pericardial effusion

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"On behalf of IMPI-2 Investigators"

Keywords: Pericardial effusion, pericardiocentesis, fibrinolysis, pilot trial

Abstract

Background: Effusive pericarditis is a cause of cardiovascular morbidity and mortality in Africa and other regions with high tuberculosis and HIV burden. The ***I***nvestigation for ***M***anagement of ***P***ericardit***i***s (IMPI)-2 is a trial designed to determine whether intrapericardial alteplase [IA] can facilitate pericardiocentesis to improve outcomes.

Objectives: The primary objectives are: *Phase1*: to determine the safe dose of IA for complete drainage of pericardial effusion; and *Phase 2*: to evaluate the feasibility of a large randomized controlled trial [RCT] to assess the effects of a safe dose of IA vs usual care in reducing tamponade or pericardial constriction over 12 months.

Study design: This was a *two-phase* study design—*phase 1* is an open-label one arm dose-finding study, followed by *phase 2* which is a pilot RCT.

Population: For both phases, we recruited adult patients ≥18 years with confirmed pericardial effusion and no contraindication for fibrinolysis.

Methods: ***Phase 1:*** *Interventions:* We allocated patients in sequence to 3 escalating doses of IA based on safety profile—1mg, 10mg, and 50mg.

Outcome: Maximum dose, with no minor or major bleeding.

Phase 2**:** Patients were randomised using 1:1 ratio to pericardiocentesis by use of 50mg of IA (*Intervention*) vs usual care, defined by pericardiocentesis at the discretion of the treating physician (*Control*). The primary *feasibility outcomes* (criteria for success of feasibility) include recruitment rate (3-5/month), adherence rate to study protocol (≥95%), completion of case report forms (CRF) within 24 hours of recruitment (≥95%), and adherence to follow-up (≥95%).

Results: ***Phase 1***: We recruited 12 patients—mean (standard deviation [SD]) age of 38 (16) years, and sequentially them to allocated 1mg (3 patients), 10mg (3 patients), and 50mg (6

patients) of AI. Zero out of 12 (0%): 95% confidence interval: (0%,3%) had no minor or major bleeding in all three doses.

Phase 2: 132 patients randomized to 50mg IA (n=64) and usual care (n=68). The median (SD) of age was 45 (14) years, 45% (58/132) female, and 52% (68/132) HIV positive. Recruitment rate was 4-5 patients/month over the 16 months with 97% adherence to protocol, CRF completion rate was 88.5%, and overall adherence to follow-up was 81%.

Conclusion: 50mg IA was safe for complete drainage of pericardial effusion. The results also show that it will be feasible to recruit, randomise, completely drain the effusion, and follow up patients over 12 months in the main trial.

Trial Registration: Clinical Trials. gov (NCT02673879).

Funding: South African Medical Research Council.

5. Introduction

5.1.1 The burden of tuberculous pericarditis and lessons from IMPI-1:

Tuberculous Pericarditis is a recognised cause of heart diseases especially in Africa and in regions with a high tuberculosis burden (Lange and Hillis 2004; Imazio, Mayosi, et al. 2010). As much as up to 10% of hospital admissions for heart failure in Africa is due to pericarditis (Maharaj 1991; Oyoo and Ogola 1999), and over 90% of these are related to tuberculosis (Adler, Charron, Imazio, Badano, Barón-Esquivias, Bogaert, Brucato, Gueret, Klingel, Lionis, et al. 2015). The epidemics of HIV/AIDS have further increased the prevalence of tuberculous pericarditis worldwide (Mayosi, Wiysonge, Ntsekhe, Volmink, Gumedze, Maartens, Aje, Thomas, Thomas, and Awotedu 2006). The two common complications of pericarditis are cardiac tamponade and pericardial constriction. Management of these complications often requires cardiothoracic surgery which is not readily available in most of the high burden communities.

The ***I***nvestigation for *m*anagement of *p*ericardial disease ***i***n Africa (IMPI) trial was conceptualised to research for interventions to improve outcomes of patients with pericarditis. IMPI-1 the first randomised control trial (RCT) was conducted in 19 hospitals from 8 African countries between 2009 and 2014 (Mayosi et al. 2014). It was an investigation of the role of adjunctive steroid and immunotherapy in reducing the primary composite outcome of death, constrictive pericarditis and cardiac tamponade requiring pericardiocentesis among patients with tuberculous pericarditis (Mayosi et al. 2014).

At the end of the study, among patients with definite or probable TB pericardial disease, four broad conclusions were drawn: (a) The use of Prednisolone and *Mycobacterium indicus pranii* had no significant effect on the combined outcome of death from all causes, cardiac tamponade requiring pericardiocentesis or constrictive pericarditis. (b) Both therapies led to an increased risk of HIV-associated malignancy; (c) The use of prednisolone reduced the incidence of constrictive pericarditis and hospitalisation; (d) The beneficial effects of prednisolone on

constriction and hospitalisation were similar in HIV-positive and negative and HIV-negative patients.

5.1.2 Why is there a need for another Randomised Control Trial?

Despite the growing body of knowledge on pericarditis, the disease remains a great source of morbidity and mortality in the world, especially among the more impoverished communities (Mayosi et al. 2008b). The result of IMPI-1 trial immensely contributed to science and understanding of tuberculous pericarditis. However, the finding of increased incidence of HIV related malignancies and the inability of either corticosteroid use or *mycobacterium indicus pranii* immunotherapy to reduce the primary composite outcome gave rise to a need to look for an alternative intervention which could improve major adverse pericardial outcomes.

Well-designed randomised control trial (RCT) provides the best source of evidence to influence practice; therefore, we reasoned that asking further questions through well-structured RCT was the right way to go in the quest to find answers to intervention to reduce pericarditis outcomes.

5.2 What is the rationale for using a fibrinolytic agent to facilitate pericardiocentesis?

Chapter one of the thesis provides a comprehensive review of the literature on evidence of the use of fibrinolysis in pericarditis, the rationale for its use, its mechanism of action and potential side effects. In summary, the reaction of the body's immune system to fight insults to the pericardium is the cause of exudation of fluid which ultimately results in the accumulation of fluid in the space (Burgess et al. 2002; Maisch, Maisch, and Kochsiek 1982). These inflammatory insults to the pericardial space attract leucocytes; and activated leucocytes promote coagulation, leading to the formation of fibrin (Roberts 2005). The deposition of fibrin in the area is the cause of pericardial adhesion, thickening, and loculation of effusion (Brockington, Zebede, and Pandian 1990; Mayosi, Burgess, and Doubell 2005).

The use of fibrinolysis in pericarditis was first documented in the literature over 60 years ago (Adie and Childress 1951a; Barnett et al. 2011;), and there is research evidence which suggests that the formation of fibrin is the cornerstone of the pathogenesis of both persistent inflammatory pericarditis and constrictive pericarditis (Mayosi, Burgess, and Doubell 2005). Inflammation and fibrin deposition are, therefore, a central theme in the aethio-pathogenesis of pericardial constriction and persistent loculation of fluid in the pericardial space. Fibrin may be a potential target in the management of exudative inflammatory pericarditis, such as tuberculous, purulent, neoplastic and auto-immune pericardial effusion. Finding a way of addressing fibrin deposition may, therefore, provide the answer to persisting pericardial effusion and its sequelae of constriction.

There are Isolated case reports on the use of intrapericardial fibrinolytic agents as rescue therapy for pericarditis in both animal studies and humans (Bigham et al. 2008; Dybowska et al. 2015). However, there has not been a large-scale randomised control trial to establish their role in a large population.

5.3 The rationale and design of IMPI-2 and the reason for a two-phased study

The second investigation of the management of pericarditis (IMPI-2) trial, is an RCT designed to test the efficacy and safety of complete percutaneous pericardial drainage facilitated by intrapericardial tissue plasminogen activator (t-PA) compared to conventional pericardiocentesis when indicated in adults with a large pericardial effusion due to tuberculous and non-tuberculous pericarditis. IMPI-2 uses a generic form of t-PA called alteplase in the trial.

The IMPI-2 trial hypothesizes that among patients with large pericardial effusion who receive treatment for the underlying cause of pericardial disease, those who are randomised to receive intrapericardial alteplase (IA) to ensure complete pericardial drainage, will have a 35% reduction in the combined endpoint of cardiac tamponade requiring pericardiocentesis and constrictive

pericarditis, compared to conventional pericardiocentesis when indicated. The RCT addresses two broad research questions:

a) among patients with large pericardial effusion due to tuberculous and non-tuberculous causes, is complete pericardiocentesis facilitated by use of intrapericardial fibrinolysis effective in reducing the combined outcome of death, cardiac tamponade requiring pericardiocentesis and constrictive pericarditis compared to standard percutaneous pericardiocentesis when needed over 12 months?

b) among patients with large pericardial effusion due to TB and non-TB causes, does complete pericardiocentesis using intrapericardial fibrinolysis increase the incidence of significant bleeding, other non-major bleeding and other adverse events compared to standard pericardiocentesis when required over 12 months.

We structured this study in two phases; *Phase 1* was a dose-finding study to determine a safe and appropriate dose of IA to facilitate complete percutaneous pericardial drainage. *Phase 2* was a pilot RCT designed to evaluate the feasibility of conducting a large multicenter trial and being able to recruit adults with pericardial effusion at an appropriate rate and to follow them up for 12 months (IMPI-1 Pilot trial).

Phase 1 was a prelude for the pilot RCT and was like phase 1 of a clinical trial (the foundation of any successful drug development process used to establish adequate dose and schedule for efficacy). In this study, the phase was used to evaluate the scientific basis for the study hypothesis by first ascertaining the safety and efficacy of IA in patients with large pericardial effusion. Through the dose-finding study, we determined the correct dose for IA in patients with pericardial effusion. Parameters under the purview of the dose-finding study included the starting dose, rate of dose increment, the dose escalation method, number of patients needed per dose level, specification of dose-limiting toxicity, the definition of maximum tolerated dose (MTD) and patient selection.

The goal of the pilot was to lay the foundation for the larger trial, by providing information for planning and justification of a planned randomised control trial. We did this through evaluation of the organisational readiness on such parameters as the number of participants expected, the willingness of these participants and their referring physicians to be part of the trial, and the rate of recruitment. Also, the pilot is planned to provide an opportunity for test running the trial processes such as randomisation, compliance with the protocol, data collection tool/questionnaire, recruitment and consent process. Other parameters will include the acceptability of the intervention, selection of the most appropriate primary outcome measures as well as the ability to identify events of interest and follow-up related to the process.

5.4 Study research questions

***Phase-1*:** What is the safe dose of intrapericardial alteplase (IA) that can effectively facilitate complete pericardiocentesis in patients presenting with large pericardial effusion without a] altering systemic markers of coagulation, and b] causing clinically detectable minor or major bleeding?

***Phase-2*:** Is it feasible to recruit participants with large pericardial effusion, adhere to all aspects of the study protocol and follow up the participants for 12 months, well enough to meet the standards required to complete the randomised controlled trial?

5.5 Objectives

Phase 1: The primary objective is to determine the safe dose of IA for complete drainage of pericardial effusion.

Phase 2: The primary objective is to evaluate the feasibility of a large randomised controlled trial [RCT] to assess the effects of a safe dose of IA vs usual care in reducing tamponade or pericardial constriction over 12 months.

The secondary objectives of *Phase 2***:** Identification of all intervention related and other adverse events, such as bleeding, adverse reaction from trial medication, unexpected adverse events, re-accumulation of effusion and hospitalisation.

5.6 Study Population

For both phases, we recruited adult patients ≥18 years with confirmed large pericardial effusion ((i.e. ≥1cm echo-free space anterior to the right ventricle in diastole) and no contraindication for fibrinolysis. Eligible patients were also required to express willingness to participate for the full duration of the trial and provide written informed consent. Participants were excluded in the presence of uremic pericarditis **(**patients undergoing dialysis or urea level more than 21.4 mmol/L), the presence of thrombocytopenia pregnancy and any contraindication to use of fibrinolysis.

5.7 Study design and Methodology

A *two-phase* study design—*phase 1* is an open-label one arm dose-finding study, followed by *phase 2* which is a single blinded (participants) pilot randomised control trial.

5.7.1 Methods:

Phase 1 *(Dose-finding): Interventions:* We allocated patients in sequence to 3 escalating doses of IA based on safety profile—1mg, 10mg, and 50mg.

Outcome: Maximum dose, with no minor or major bleeding.

Phase 2 *(Pilot RCT)*: We randomised patients using 1:1 ratio to pericardiocentesis by use of 50mg of IA (*Intervention*) vs usual care, defined by pericardiocentesis at the discretion of the treating physician (*Control*).

The primary *feasibility outcomes* (criteria for success of feasibility) include recruitment rate (3-5/month), adherence rate to study protocol (≥95%), completion of case report forms (CRF) within 24 hours of recruitment (≥95%), and adherence to follow-up (≥95%).

The secondary safety outcomes for *Phase 2* include all intervention related and other adverse events, such as bleeding, adverse reaction from trial medication, unexpected adverse events, re-accumulation of effusion and hospitalisation. Information on the detailed efficacy and safety of intervention were meant exclusively for the trial safety monitoring board.

Managing physicians from different referring centres sent patients for the trial based on clinical suspicion of pericardial effusion. They were screened to confirm eligibility by 2-D echocardiography, electrocardiogram, full blood count, electrolyte, creatinine, urea estimation and pregnancy test if female (see study flow diagram). Eligible patients provided informed consent, and we used the University of California San Diego Brief Assessment of Capacity to Consent (UBACC) questionnaire modified for the IMPI pilot trial to evaluate their comprehension of the consent information (Jeste et al. 2007). Randomisation using 1:1 ratio to pericardiocentesis by use of 50mg of IA (*Intervention*) vs usual care, defined by pericardiocentesis at the discretion of the treating physician (*Control*). The trial team was automatically alerted to the outcome of randomisation and pericardiocentesis was arranged and carried out at either the catheterisation laboratory or procedure room. Pericardiocentesis was done using the subcostal approach and aspiration to dryness confirmed by echocardiography (less than 1cm echo-free space over the right ventricle at the end of diastole). Samples were sent out for analysis and those in the intervention arm were given 50mg of intrapericardial alteplase and catheter flushed with 7ml of normal saline while those on routine arm had the catheter removed as per local site practice

Patients subsequently had a chest x-ray and post-procedure haemoglobin estimation; we then transferred them to the ward for observation and appropriate treatment. Those in the routine arm were discharged within 24 to 48 hours if stable, while those on alteplase arm had another 2-D echocardiography at 2 hours post procedure and repeated aspiration to dryness. The

protocol stipulated that, if at 2 hours post-aspiration, 2-D echocardiography revealed significant re-accumulation of fluid and aspiration to dryness is not achieved, the second dose of 50mg alteplase should be given and the entire steps repeated.

We managed all participants in liaison with the medical unit and discharged them if stable, in 24-48 hours with a detailed follow-up plan and appropriate referral were made based on the clinical status.

5.7.2 Ethical Review

The IMPI-2 trial is approved by the Faculty of Health Sciences Human Research Ethics Committee of the University Cape Town (HREC REF 370/2015) and the South African Health Products Regulatory Authority [formally Medicine Control Council of South Africa] (20150723). The IMPI-2 trial is registered with clinical trials.gov (NCT02673879).

5.7.3 Data analysis

For *phase 1*, using a previously validated dose-finding sample size calculation method (Le Tourneau, Lee, and Siu 2009), we arrived at 12 participants as the required sample size to ascertain the safe dose of IA to facilitate complete drainage. Simple descriptive analysis was used to present the data. The required sample size for *Phase 2* of the study is 218; however, we based the sample size of this preliminary report on a convenient sampling for feasibility evaluation. We analysed all clinical measures on an intention-to-treat basis. Descriptive statistics were calculated for all variables over the six-time points (baseline, two weeks, six weeks, three months, six months and twelve months). Continuous variables were reported as a median and interquartile range (IQR) and compared using student T-test for continuous variables, while categorical variables were reported as count (%) and analysed using Chi-

square test for categorical variables. Statistical significance was taken at the p= 0.05 level. Data analysis was performed using Stata version 14.2 (StataCorp, College Station, TX, USA).

5.8 Results

In figures 5.1 and 5.3 the study flow charts for both phases of the study are presented, while Table 5.3 shows the key findings of the study.

Phase 1

We recruited a total of twelve patients with a mean age (standard deviation) of 38 (16) years, 58.3% (7/12) were females, and approximately 42% (5/12) were HIV positive (See Table 5.1 for the timing of recruitment).

The patients were systematically allocated to escalating doses of IA, starting at a minimal dose of 1mg (3 patients) 10 mg (3 patients) and 50mg (6 patients). None of the 12 patients (0%) [95% confidence interval (0%,3%)] had minor or major bleeding. Only one patient had systemic IA concentration of 0.5ng/ml (excess of 10ng/ml is required to induce systemic plasmin generation) [Figure 5.2]. The baseline alteplase values following intrapericardial administration remained unchanged for all the study participants different from what obtains following parenteral administration.

Phase 2

We screened 300 patients in the two active sites (Cape Town and Mthatha); 132 (44%) patients were recruited, which was 60% of projected recruitment in 16 months; 48.5% (64/132) into alteplase arm and 51.5% (68) into the routine arm. Cape Town began recruitment four months before Mthatha and achieved 118% of our planned recruitment, at an average of 4-5 patients per month (Figure 5.4 and Figure 5.5). Four of the patients in the alteplase arm could not get

the intervention due mainly to the failure of pericardiocentesis, and ultimately 46.2% had intrapericardial alteplase. The median age (standard deviation [SD]) was 45 (14) years, and females constituted 44.6% (58/132) of the study population. There were no significant differences in the baseline characteristics between the two arms.

There was a failure to administer the drug in 3% (4/130) of participants. The primary reason for this deviation from protocol was a failure of percutaneous pericardiocentesis and none placement of pigtail catheter in the pericardial space. In one case excessive bleeding intra-procedure made the physician abandon alteplase administration. Inadequate history from 2 participants resulted in the wrong recruitment of patients who were ineligible for the trial; however, no harm occurred. These alterations resulted in 97% adherence to study protocol. The timing between randomisation and intervention was within 24 hours in over 90% of participants.

The increasing re-accumulation of effusion especially in the alteplase arm within 24-48 hours post pericardiocentesis led to slight modification of the protocol concerning patients on the alteplase arm. Instead of removal of pigtail catheter after repeat echo and aspiration at 2 hours, we left the catheter for 24 hours and re-evaluated patients next day for evidence of re-accumulation and re-aspiration if indicated before removal of the catheter.

The overall adherence to follow-up was 80.9% (We This percentage was based on a ratio of the actual number of visits recorded versus expected follow-up visit [364/450]). It was maximum at two weeks and three months (85.6% and 83.3% respectively). By twelve months there was a significant drop-out rate and adherence to follow-up was 62.9% (Table 5.2). There was better adherence in the routine arm compared to intervention. At the time of this preliminary report, we lost 10% of the study population to follow-up (13/130). Three of the patients relocated to other provinces, two left the republic being foreign nationals, while another three were alive and receiving anti-tuberculous medications from other hospitals but refused to present for trial follow-up. We contacted participants by telephone or used field workers to trace the participant's contact address when they missed a follow-up visit despite prior reminders. A patient is deemed

to have been lost to follow up if he/she fails to turn up for appointment consecutively after repeated telephonic reminders and confirmation that the patient is alive.

CRF completion rate was 88.5%; it varied between the two study sites as shown in Figure 5.6. Cape Town site had no personnel to enter data from patients' files, resulting in 80% CRF completion rate compared to 97% in Mthatha.

Secondary Safety Assessment:

We recorded no case of minor or major bleeding attributable to IA wa**s,** and there were no recorded adverse events.

Other Pilot Trial Results:

Approximately 52.7% (68/130) were HIV positive, TBP accounted for 91% of the presumptive diagnosis in the study population but was only conclusively proven in 26% (33/130) [15.4 % had culture-positive TB, and 10% were culture negative respectively].

Tuberculosis was the cause of pericarditis in 91.5% based on the finding of the culture-positive specimen in 15.4% (20/130), gene expert positive in 10%, ADA> 30 IU/L in 34.1% and suspected TB based on history in 31.8% (41/130). We obtained a histological diagnosis in six of the eight patients who had malignancy (four small cell lung adenocarcinoma, one blast phase Non-Hodgkin's lymphoma, one primary cardiac tumour).

5.9 Discussion

The results of *Phase 1* of this two-phase study showed that at a dose of 50mg, intrapericardial alteplase was safe in facilitating complete drainage in patients presenting with large pericardial effusion. No adverse events such as minor bleeding occurred at any of the doses employed in

the phase, and the trial process was adjudged to be safe for the commencement of phase 2 of the study.

In *Phase 2*, the target of recruitment was surpassed at an average of 4-5 patients per month, and we established that the study was feasibility (Figure 5.4 and Figure 5.5). However, we could not meet the projected adherence rate to study protocol with 3% deviation. Also, the CRF completion rate fell short of expectation in one of the sites. The longer the participants were in the trial, the less likely they were to continue follow-up.

The following observations were drawn from this preliminary report to allow improvement of design and conduct of the main study: The administration of IA during pericardiocentesis; retention of pigtail catheter for up to 48 hours after IA administration to prevent patients representing with re-accumulation. Others include the combined use of electronic and paper CRFs, reviewing randomisation of patients with malignant effusion and use of data capturers to enter data.

The study in the first 16 months covered by this preliminary report recorded a high attrition rate, like findings in the IMPI-1 study (Mayosi et al. 2014), though in it, injection side effect from mycobacterium indici was given as the reason. The CRF completion rate was also reduced, especially in the Cape Town trial site. One reason for this finding was the switch from originally intended electronic data capture to use of paper case report forms without making provision for any staff to capture the data. We hope that in the main trial adequate funds are mapped out to engage desk officers to capture the data so that the research fellow can devote more time to trial-related procedures. We introduced some measures to improve follow-ups such as telephonic reminders and contact tracing. A substudy, the **I**nformed **C**onsent **C**omprehension study (ICC study), was also initiated to improve consent comprehension.

5.10 Conclusions

Analysis of IMPI-2 trial dose-finding study and the review of the experience from the first 132 patients recruited to the IMPI-2 pilot trial led us to the following conclusions towards the conduct of the main IMPI-2 trial: 1) At 50mg, intrapericardial alteplase was safe in facilitating complete pericardiocentesis with no compromise of patient's safety measured by the occurrence of minor or major bleeding. 2) Conduct and completion of the IMPI-2 randomised controlled trial is feasible. Based on the findings of this preliminary study, it is possible to recruit, randomise completely drain and follow up patients in line with the protocol of the study. However, to minimise the incidence of re-accumulation of pericardial fluid following the use of IA, initial monitoring before removal of pigtail catheter should be delayed for 48-72 hours. In recruiting patients, consideration should be given towards exclusion of patients in terminal stages of malignancies as such may not have a good outcome with IA. Also, the patient's education and reiteration of consent information, as well as using contact tracing, can improve adherence to protocol.

The need to ensure the later led to development of the informed consent comprehension study through the use of University of California Brief Assessment of Capacity to Consent (UBACC), with primary objective of evaluating the feasibility (defined as the acceptance of the use of UBACC among at least 50% of IMPI-2 pilot trial participants for informed consent comprehension evaluation) and the utility of the UBACC as a training tool for iterative consent administration among participants. This study is presented in chapter 6.

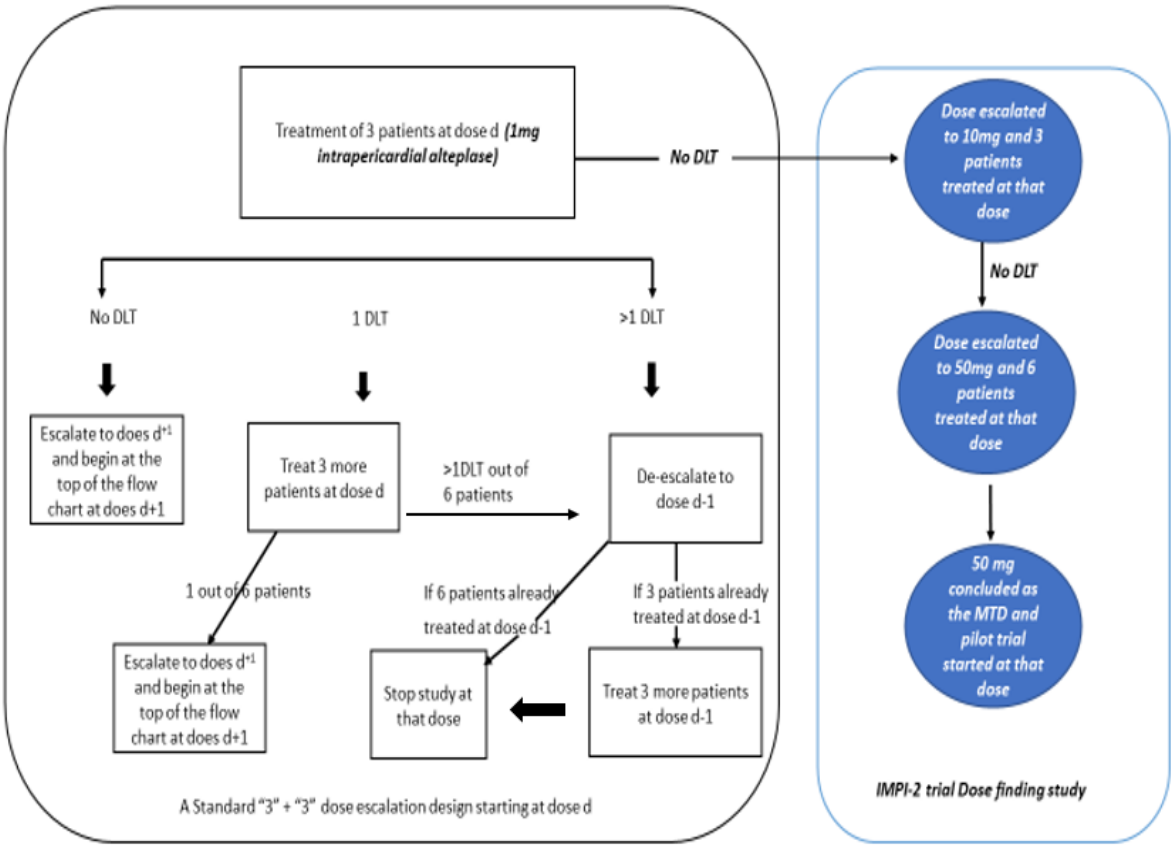


Figure 5.1: The dose escalation flow chart, IMPI-2 dose-finding scheme highlighted in **bold**

(DLT= Dose-limiting toxicity; MTD= Maximum tolerated dose)

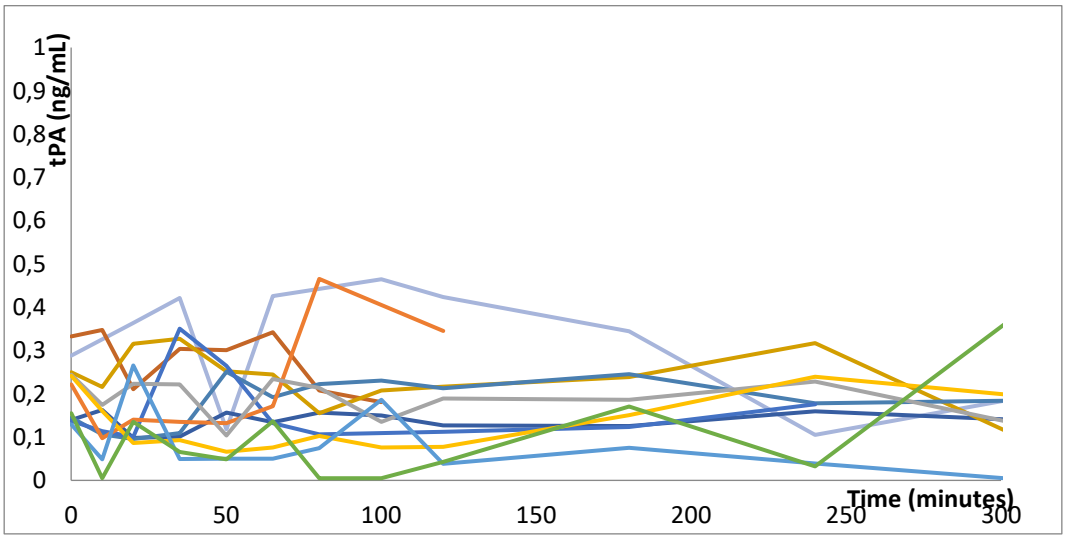
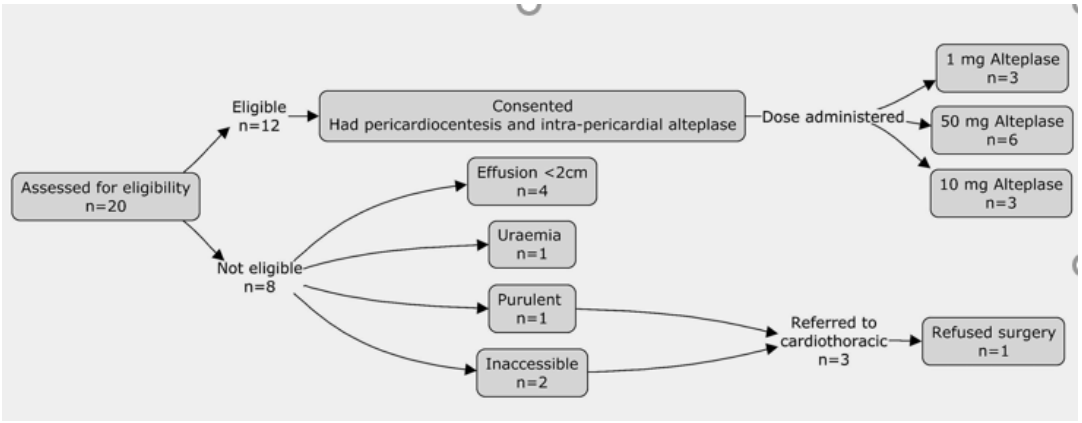


Figure 5.2: Alteplase concentration in the dose-finding study

Table 5.1: Baseline characteristics of Dose-finding study participants	
Variables	**N=12**
Female sex-no. (%)	7 (58.3)
Age- mean (SD)	38 (16)
Referral Hospitals-no. (%)	
• New Summerset Hospital	3 (25.0)
• Groote Schuur Hospital	3 (25.0)
• Mitchel's Plain District Hospital	2 (16.7)
• Hiedeveld Emergency Centre	1 (8.3)
• Khayelitsha District Hospital	1 (8.3)
Co-morbidities- no. (%)	
• Human immunodeficiency (HIV)	5 (41.7)
• Malignancy-related	2 (16.7)
• Diabetics Mellitus	2 (16.7)
Mortality- no. (%)	
• Cerebrovascular accident	1 (8.3)
• Pulmonary Embolism	1 (8.3)
• Metastatic diseases	1 (8.3)



Dose-finding study

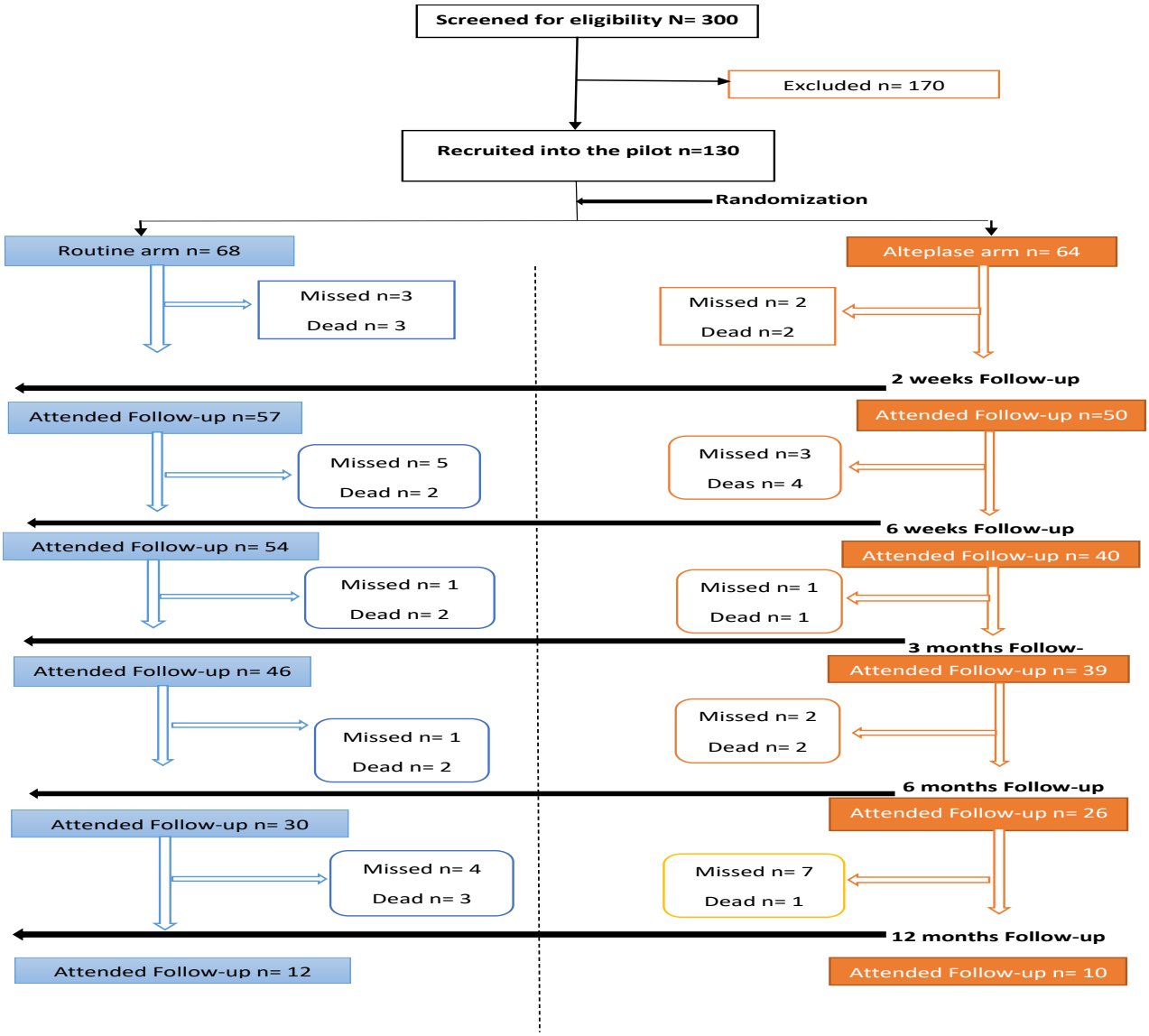


Figure 5.3: Study flow diagram

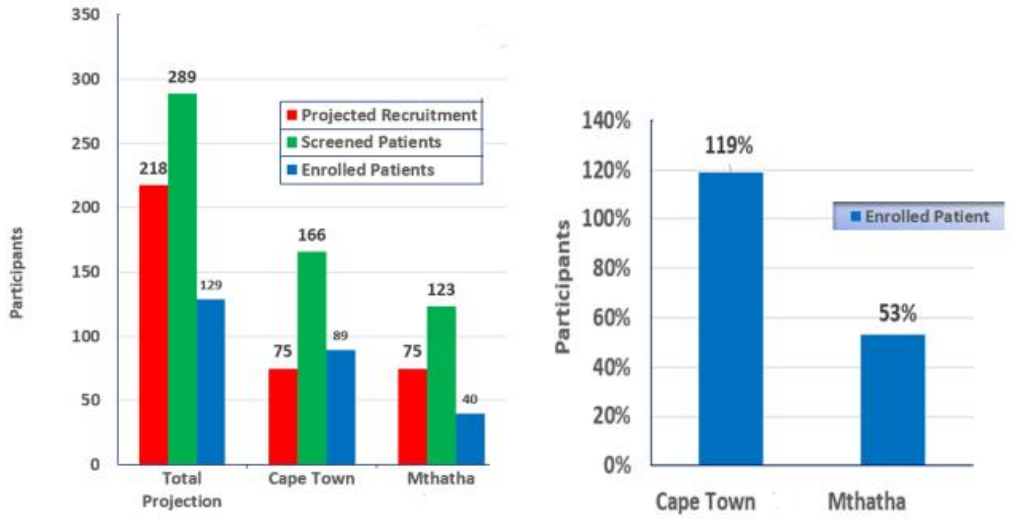


Figure 5.4: IMPI-2 Pilot Screening (Projected versus actual)

Table 5.2: Baseline Characteristics of the Subgroup[¶]		
Variables	**Alteplase n=64**	**Routine n= 68**
Female sex – no. (%)	32 (50.0)	26 (39.4)
Age -year	47 (34-60)	44 (33-57)
BMI – Kg/m^2	22.4 (15.8-55.0)	21.8 (14.6-34.2)
NYHA Class – no. (%)	14 (21.9)	14 (21.1)
Class I	11 (17.2)	21 (31.8)
Class II	19 (29.7)	17 (25.8)
Class III	20 (31.3)	14 (21.2)
Class IV		
Systolic Blood Pressure - mmHg	116 (106-125)	114 (105-122)
Diastolic Blood pressure - mmHg	74 (66-81)	74 (68-83)
Pulse rate – beats/min	106 (93-120)	103 (92-113)
Duration of symptoms – days no. (%)		
<30 days	46 (71.9)	51 (77.3)
>30 days	18 (28.2)	15 (22.7)
Left ventricular function – no. (%)		
Normal	51 (83.6)	59 (93.7)
Impaired	10 (16.4)	4 (6.4)
HIV Status		
Positive	33 (52.4)	35 (53.6)
Negative	30 (47.6)	31 (47.0)
Size of effusion- no. (%)		
Large >2cm	50 (82.0)	53 (85.5)
Medium1-2cm	10 (16.4)	8(12.9)
Small <1cm	1 (1.6)	1 (1.6)
Characteristics of Fluid – no. (%)		
Bloodstained	35 (62.5)	34 (55.7)
Serosanguinous	12 (21.4)	17 (27.9)
Serous	8 (14.3)	9 (14.8)
Purulent	1 (1.8)	1 (1.6)
The total volume of fluid aspirated - ml	1.1 (0.84-1.65)	0.89 (0.60-1.30)
CD4 cell count		
<200 cells/mm^3	14 (63.6)	17 (70.8)
>200 cells/mm^3	8 (36.4)	7 (29.2)
Total WBC	6.8 (4.7-9.6)	7.2 (5.7-9.9)
Haemoglobin	10.7 (9.0-11.7)	10.7 (9.4-11.9)
Mortality – no. (%)	11 (17.2)	8 (14.7)

[¶] Continuous variables presented as median (IQR). BMI-Body mass index; NYHA- New York Heart Association; WBC- White Blood Cell Count

Table 5.2: Continues

Variables	Alteplase n=64	Routine n= 68
Cause of Effusion- no. (%)		
Tuberculosis		
Confirmed (Culture or GXP)	17 (26.6)	16 (24.6)
Probable (ADA>30 IU/L)	19 (26.7)	25 (38.6)
Suspected	22 (34.4)	19 (29.2)
Malignancy	4 (6.25)	4 (6.15)
Purulent pericarditis	1 91.56)	1 (1.54)
Connective tissue disease	0 (0.0)	1 (1.54)
Adherence to Follow-up no. (%)		
- Two weeks	50 (83.3)	57 (87.7)
- Six weeks	40 (74.1)	54 (88.5)
- Three months	39 (79.6)	46 (86.8)
- Six months	26 (76.5)	30 (76.9)
- Twelve months	10 (58.8)	12 (66.7)

ADA-Adenosine deaminase assay; GXP- Gene expert

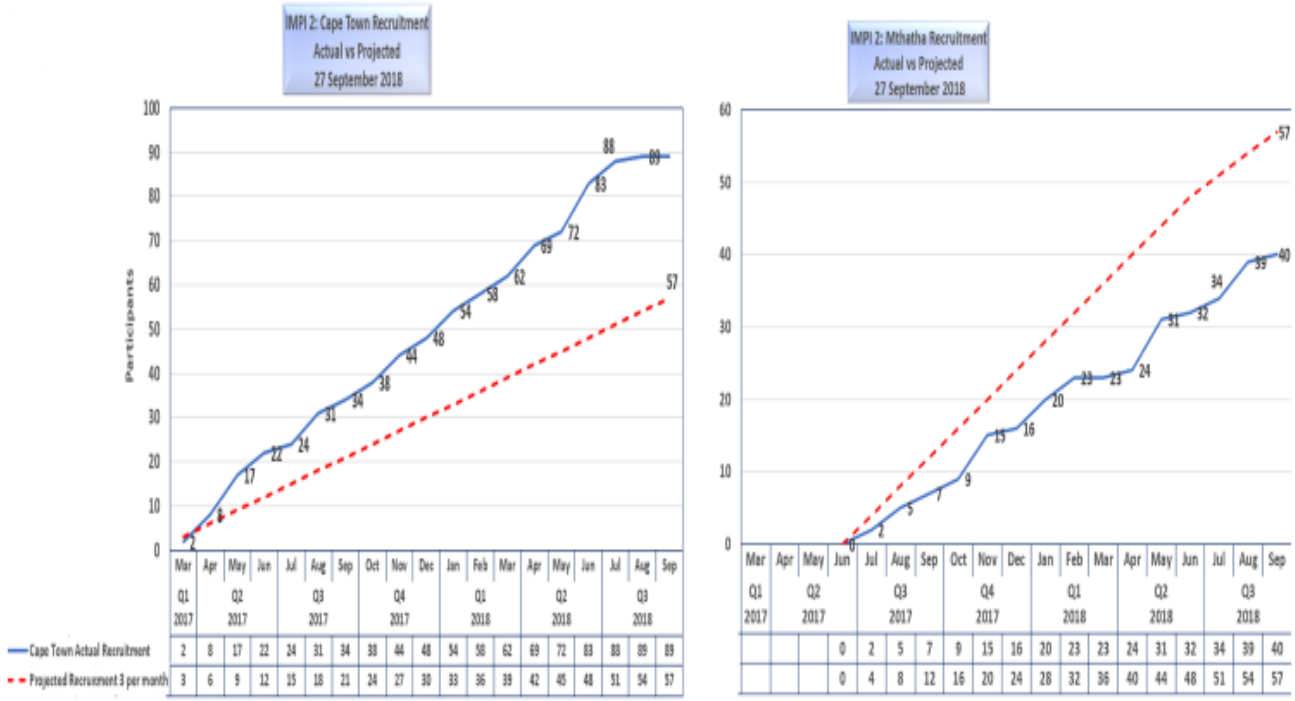


Figure 5.5: Recruitment performance

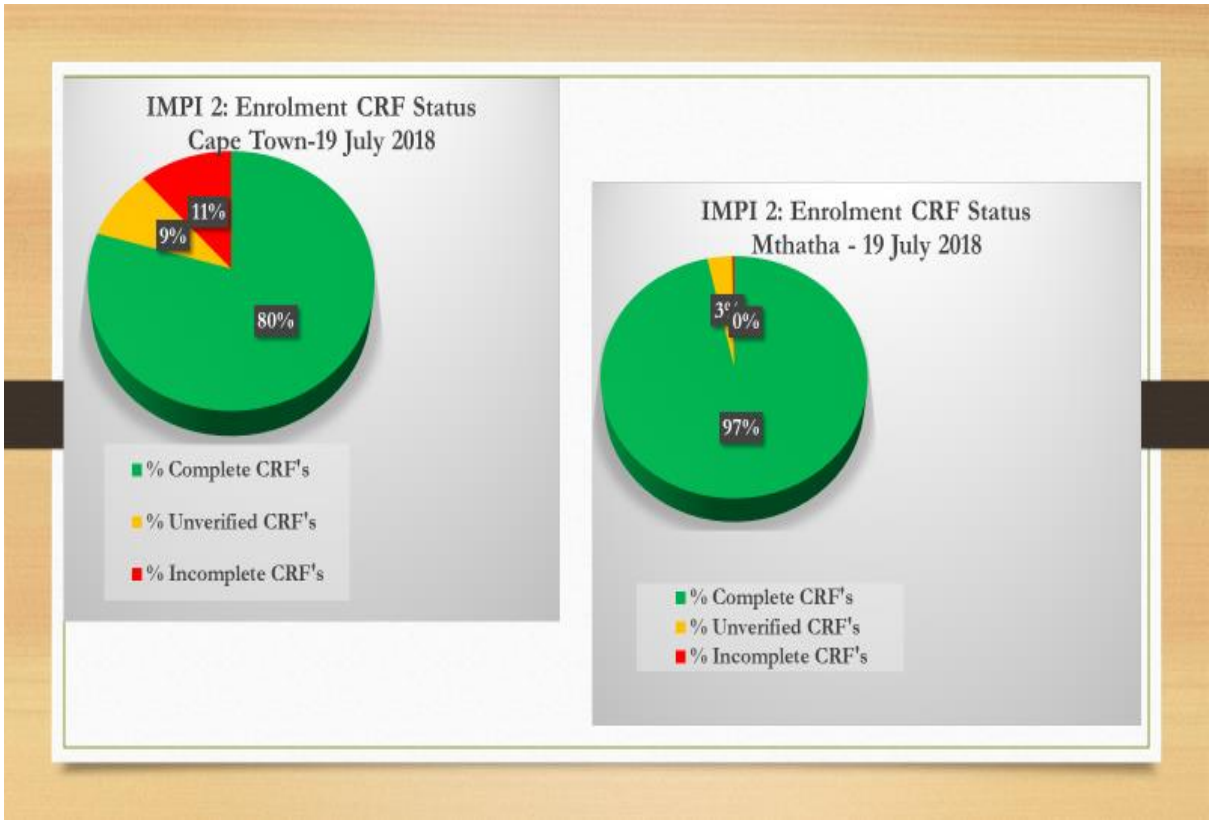


Figure 5.6: CRF completion rate July 2018

Table 5.3 Study Key Messages
Phase 1 Key findings on dose-finding • Zero percentage of patients had minor or major bleeding • 50mg of intrapericardial alteplase is a safe dose for complete drainage of pericardial effusion. *Phase 2* Key findings on feasibility (criteria for success of feasibility) • Recruitment rate was 4-5 patients/month over the 16 months (3-5/month), • 97% adherence to protocol (≥95%), • CRF completion rate was 88.5% (≥95%), and • Overall adherence to follow-up was 81% (≥95%). It is feasible to recruit, randomise, completely drain the effusion, and follow up patients over 12 months in the main trial.

Dedication

We dedicate this work to the loving memory of the late Prof BM Mayosi, supervisor, mentor and pioneer of the IMPI study.

Acknowledgement

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CHAPTER SIX
Piloting a Tool for Informed Consent Comprehension in a Cardiovascular Clinical Trial in South Africa: An IMPI-2 Pilot trial Substudy

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ABSTRACT

Background

Informed consent (IC) is critical for research involving humans. In the pilot study for the second investigation of the management of pericarditis (IMPI-2), we used the University of California Brief Assessment of Capacity to Consent (UBACC) to determine the feasibility of administering the UBACC during the IC process for IMPI-2. We also explored the potential impact of UBACC to improve informed consent comprehension (ICC) over time, and factors associated with ICC.

Methods

Consenting trial participants were administered the UBACC four times over six months; we recorded responses at each visit. A UBACC score of ≥25 was considered adequate comprehension.

Outcomes

The primary feasibility outcome was acceptance of UBACC evaluation, with success measured by ≥50% of participants accepting the tool. The secondary outcome was ICC defined by UBACC score ≥25. We used univariate logistic regression to explore comprehension over time and factors associated with UBACC score ≥25.

Results

Eighty-one participants (91% of invited participants) accepted use of the UBACC. Comprehension improved with time, the odds of passing the evaluation at six months compared to baseline was higher by 39% (OR 1.39, 95% C.I 1.17-1.65, p <0.001). Factors associated with a lower ICC were the use of interpreters and low education level (OR 9.17; 95% C.I 2.11;39.8; p-value 0.003).

Conclusion

Use of UBACC as a tool to evaluate ICC in a randomised clinical trial is feasible; using it as a training tool repeatedly during follow-up has the potential to improve ICC over time.

6.1 INTRODUCTION

Informed consent (IC) is a voluntary agreement by participants to be part of a research project, following the presentation of sufficient information by a qualified member of the research team (Health, principles, and research 1975). It is a crucial component of research, involving availing the participant with accurate information on their condition, purpose, risks and benefits of the study, the current standard of care and available alternative methods. A robust informed consent process ensures that participants understand the information provided, give a voluntary decision and suffer no negative consequences should they refuse to participate (Emanuel, Wendler, and Grady 2000; Marshall et al. 2006) However, the extent to which these requirements are achieved often remains a matter of researcher judgement in which empirical evaluation during the consent process has little place (le Roux-Kemp 2011). Balancing completeness versus simplicity is a real challenge in the preparation of patient information materials, especially in low and medium-income countries (LMICs). Social factors such as poor literacy and increased vulnerability confront the population when asked to participate in research they do not fully understand. The Declaration of Helsinki requires researchers to ensure the comprehension of information they give to potential participants (Association 2013).

A range of tools have been developed in clinical research to assess the understanding of informed consent, such as structured questionnaires (Flory and Emanuel 2004) and quizzes (Lindegger et al. 2006). In evaluating comprehension, any instrument used should enhance the decisional capacity of participants through an understanding of the critical elements of the research process.

One such tool is the University of California San Diego Brief Assessment of Capacity of Consent Questionnaire (UBACC). It is a screening tool consisting of 10 items scored on a scale of 1 to 3, with 1 reflecting an inadequate response and 3 indicating an intelligent response. An intermediate score of 2 may be used for partially appropriate responses or uncertainty even after re-explanation [The original UBACC (Jeste et al. 2007) tool's scale was from 0 to 2, however, in our current study we shifted the scale for ease of analysis]. The UBACC was initially

designed for use in evaluating capacity to comprehend during recruitment into psychiatric research and could be a helpful tool in ensuring understanding of informed consent through repeated teaching and evaluation of comprehension among research participants. The UBACC tool screens for participants' appreciation and understanding of research study elements including purpose, protocol/procedure, risk-benefit and voluntary nature of participation (Jeste et al. 2007). It has been used in research on schizophrenia (Jeste et al. 2008), neurocognitive conditions (Duron et al. 2013), HIV (Doyle et al. 2016) and, recently, in genomics of schizophrenia research in South Africa (Campbell et al. 2017), and shown to be a useful tool for improving understanding of research elements. We decided to evaluate the feasibility of administering the UBACC as a training tool among participants being enrolled in the second Investigation of Management of Pericardial disease pilot trial (IMPI-2). A randomised control trial (RCT) of Complete Percutaneous Pericardial Drainage Facilitated by Intrapericardial Alteplase Compared to Conventional Pericardiocentesis When Indicated in Adults with Large Pericardial Effusion due to Tuberculous and Non-Tuberculous Pericarditis. The study will test whether participants randomised to the intervention arm will have a reduction in major adverse pericardial diseases outcomes compared to those in the placebo arm. The pilot phase of the trial which was used to assess UBACC was designed to evaluate the feasibility of recruiting and retaining participants and assessing adherence to the study protocol in preparation for the larger multicenter trial.

The current study, named the **I**nformed **C**onsent **C**omprehension study (ICC study), was designed to evaluate the feasibility (defined as the acceptance of the use of UBACC among at least 50% of IMPI-2 pilot trial participants for informed consent comprehension evaluation) and the utility of the UBACC as a training tool for iterative consent administration among participants. Specifically, the study tested to see if participants will allow the use of UBACC to evaluate their comprehension and if their comprehension of information obtained during the IMPI- 2 consent process improves over time using the 'teach to goal' method (Isles 2013; Kripalani et al. 2008; Paasche-Orlow et al. 2005). The study will also examine factors associated with better consent

comprehension. To the best of our knowledge, this is the first time this kind of research has been done on clinical trials in Africa.

The hypothesis is that the use of the UBACC as a training tool will improve consent comprehension among participants of the IMPI-2 pilot trial. The primary objective of the study is the determination of the feasibility of use of the tool defined as the acceptance of the use of UBACC among at least 50% of IMPI-2 pilot trial participants for informed consent comprehension evaluation. The secondary objectives include evaluating if its comprehension improves with use of UBACC as a training tool, if informed consent comprehension improves over time and identification of factors associated with the improvement in comprehension.

The primary outcome of the ICC study is number of participants that accepted the use of UBACC for informed consent evaluation at baseline. It is important to note that the ICC substudy was conceived and approved after the IMPI-2 pilot trial had already begun. For regulatory reasons, a low UBACC score could not be used as an exclusion criterion for enrolment.

6.2. METHODOLOGY

6.2.1. Data Collection

Patients referred to the IMPI-2 pilot trial were screened for eligibility based on the inclusion and exclusion criteria outlined in the trial protocol (NCT02673879 clinical trials.gov). This includes age 18 years and above, no contraindication to fibrinolysis and presence of large pericardial effusion. Demographic data information and any previous history of involvement in a clinical trial were also collected.

Once eligibility was established, participants were taken through the IMPI-2 consent process using a standardised consent form (available in English, Xhosa and Afrikaans) [Appendix 1]. This included information on details of the study, currently available treatment, the purpose of the study, randomisation, risk and benefit of participating, follow-up plan, duration of the study,

confidentiality, voluntary participation and freedom to withdraw. An opportunity was given for questions and clarifications. We used a flow diagram to illustrate the basic concepts of pericardial effusion, pericardiocentesis, potential complications randomisation and follow-up. Those who did not understand the English language had interpreters to assist in the process.

Once the participant had no further questions, we administered the UBACC to evaluate their comprehension and recorded the total UBACC score following the first consent. Items on which the participant scored 1 or 2 were then re-explained and a further opportunity for questions given, after which the UBACC was re-administered (Figure 1). Where this was administered more than once; an average score was taken. In some situations, patients declined the UBACC evaluation after giving consent to enrolment in the IMPI-2 trial. In such instances, we evaluated them at the two weeks follow-up visit. UBACC was used as an iterative training tool and not a screening tool, and no comparison to baseline was done for people who had a UBACC greater than 25 at baseline.

At each follow-up visit (two weeks, six weeks, three months and six months), we provided the patients with all information given in the initial consent process, but without formally re-consenting. This was then followed by inquiring about new symptoms, drug use and general well-being. The patients were subsequently examined, and echocardiography was performed, followed by an assessment of comprehension using the UBACC. Where incorrect answers suggested gaps in comprehension, relevant information was provided verbally to the patients again. At the end of the process, we conducted repeat evaluations and recorded the average UBACC score for that visit. This sequence of events was a product of the fact that the ICC study was introduced as a substudy only after the pilot trial had already been approved and started.

6.2.2. Sample Size

Sample size estimation was based on the feasibility outcome of recruiting 50% of eligible pilot trial participants. Using the confidence interval (C. I) approach (Cocks and Torgerson 2013) at

95% C.I. with a prior estimate of 0.80, and a margin of error of 0.10, we would require at least 61 participants in assessing the feasibility of use of the UBACC for informed consent comprehension among IMPI-2 pilot participants (Appendix 2).

6.2.3. Statistical Analysis

Data analysis were done using STATA 14 (Stata Statistical Software College Station, TX). We reported age as a categorical variable in groups and presented all categorical variables as count (%). Bivariate logistics regression was performed for baseline and subsequent UBACC scores to identify the relationship between factors such as age, sex, level of education, use of interpreters and different UBACC scores at baseline (Appendix 3), and to determine the odds of having UBACC score ≥25 at each follow-up visit compared between baseline, as well as odds of passing the question by the interval since the last evaluation. Identification of significant predictors of outcome was done using bivariate regression models at 95% CI and p-value <0.05.

6.3 Ethical Review

The IMPI-2 trial and patient information documentation were approved by the Faculty of Health Sciences Human Research Ethics Committee of the University Cape Town (UCT HREC 370/2015) and the South African Health Products Regulatory Authority (20150723). It was registered with clinical trials.gov (NCT02673879). The ICC substudy reported in this paper was approved through an amendment to the parent study.

6.4. RESULTS

6.4.1 Data Included

From April 2017 to August 2018, we screened 300 participants for eligibility into the IMPI-2 pilot trial and recruited 128 participants in the two centres (89 from Cape Town and 39 from Mthatha). This ICC study was conducted at the Cape Town study site.

Eighty-nine participants were invited to take part in the informed consent comprehension evaluation with the UBACC. Ninety-one per cent (81/89) [95% confidence interval: 1.42; 1.65] of eligible IMPI-2 participants accepted the evaluation, with complete data for analysis available for 71 participants.

6.4.2 Descriptive Data

The demographic characteristics of the study population are displayed in Table 1. Of the 71 participants included in the analysis, there was a slight male preponderance (54.9%) and the median age (IQR) was 42 (19-77) years. Forty-nine per cent of the cohort had at least secondary level of education, 67.6% were of South African Xhosa origin and 33% needed interpreters for the interviews.

6.4.3 Comprehension of different aspects over time

The average UBACC score at baseline was 23.8. This increased with iterative learning (Appendix 4) at subsequent follow-up visits compared to baseline as shown by significant improvement at six months (Table 2). The average score for Question 1 was lowest at baseline (Table 3).

We recorded high UBACC scores in questions exploring the reason for accepting to participate in the trial (question 2), voluntariness (question 4) and financial responsibility in cases of harm resulting from participation (question 10) [Table 3].

Knowledge of the primary purpose of participation in the trial (question 3) and right of withdrawal (question 5) had a marked increase in UBACC scores at six months.

Understanding of risk of participation (question 7) either resulting from the procedure or as a side-effect of the trial intervention, remained poor. The reduced comprehension was shown by the low UBACC score throughout the study duration, which was worse at six months despite

reiteration. Comprehension of the uncertainty about the effect of the trial intervention (question 9) was low, but at six months there was a slight improvement. We did not compute the estimates of effect for the association between covariates and UBACC score

6.4.4 Factors associated with lower UBACC score

Use of interpreters (ES 0.9; 95% C.I 0.44; 1.50) and having lower than a secondary level of education (ES -0.04; 95% C.I -0.58; 0.50) was associated with a low UBACC score, most marked at six months (appendix 5). However, the study was hypothesis-generating and not powered to test significance.

6.4.5 Understanding of Specific Questions

Most participants correctly answered the question “who will pay for your medical care cost in case of trial related injuries", with a 78-90% correct response over the follow-up period. However, most participants failed to correctly answer the question “Is it possible that the treatment planned in the study may not have the expected result” despite repeated correction.

Improved comprehension was most marked with regards to their understanding of the trial concept, the benefits and that the primary focus.

6.5 DISCUSSION

Identified challenges during informed consent processes may include absence of a conducive environment, the presence of pain/distress (Britz and le Roux-Kemp 2012), poverty, low levels of education (Lavery 2007; Minnies et al. 2008) and health literacy (Adams et al. 2005) Others are the presence of investigation intervention only in the trial (Hawkins and Emanuel 2008; Mystakidou et al. 2009), insistence on signatures rather than oral agreement (Vischer et al. 2016), use of legality driven voluminous and complex consent forms (Commission 2001;

Bioethics 2005), language barriers and foreign accents of researchers (Adams et al. 2005). These challenges are worse in LMICs due to low literacy and over the years' researchers have introduced the use of tests to evaluate and improve consent comprehension in a bid to reduce the impact of the challenges.

Informed consent materials can be improved through an iterative learning process of presenting the study information, assessing a participant's understanding of the study elements, and revisiting and revising poorly understood aspects.

Tools that have been used in different studies to improve comprehension include: brief informed consent evaluation protocol (BICEP) (Sugarman et al. 2005) quality of informed consent test (QuIC) (Joffe et al. 2001) Deaconess Informed Consent Comprehension Test (DICCT) (Miller et al. 1996) Digitised Informed Consent Comprehension Questionnaire (DICCQ)(Afolabi et al. 2014) and the UBACC. Each of these tools has its challenges and is subject to different interpretations.

In this preliminary study, we showed that it was feasible to use the UBACC as a tool to track and improve ICC in an RCT. Furthermore, the use of the UBACC as a training tool was acceptable to IMPI-2 pilot trial participants. This provides further evidence to support the use of tools like the UBACC in clinical trial situations in LMICs, as previously suggested in a study in Africa among patients with schizophrenia (Campbell et al. 2017).

The purpose of the trial was not well understood at baseline, however, the level of comprehension measured by the UBACC scores improved with iterative learning over time and with repeated reinforcement over the follow-up period. The finding is evidence that reiteration improves comprehension, as seen in a study among HIV patients in Botswana (Chaisson et al. 2011). We used pictures and flow diagrams to explain different aspects of the trial and emphasis was placed on the reiteration of areas that showed low levels of comprehension, resulting in the improvement we noticed over time.

Information consistently understood about the trial were the primary purpose of recruitment being research, voluntary participation, liberty to withdraw and culpable party in events of harm. The comprehension of these aspects could enhance research integrity and strengthen adherence to follow-up in the trial.

Comprehension of information on the risk of study, randomisation and effect of the intervention was repeatedly low, despite most of the participants knowing that the primary purpose was research (question 2). We attributed this to therapeutic misconception and the complexities with explaining randomisation in LMICs; alluded to by other studies (Appelbaum et al. 1987; Joffe et al. 2001). Immediate relief from pericardiocentesis rather than the long-term complications of TB pericarditis, which the trial was designed to investigate, could be responsible for such persistent therapeutic misconceptions. Reiteration of trial information was used to improve comprehension, and this could be the reason for the marginal increase in UBACC score on question 9 at six months. The preliminary IMPI-2 pilot data result shows that visit adherence at six weeks, three months, six months and twelve months were 78%, 80%, 75% and 60% respectively. The likely explanation for the reduction in adherence with longer duration of the study, judging from the findings of the ICC study, could be that non-adherence to follow-up is related to consent comprehension. At six months the proportion of participants with high UBACC score increased, despite the reduced number of participants. Meaning that those who had poor comprehension dropped out with clinical improvement; while those who stayed on had better comprehension.

A higher level of education and non-use of interpreters for UBACC administration were associated with a higher score, consistent with what has been reported previously in the literature (Campbell et al. 2017; DuBois, Bante, and Hadley 2011; Dunn 2006).

The low UBACC score for participants who took the evaluation in Xhosa could have been due to the difficulty in explaining concepts like randomisation and research risk to the participants by the interpreters. Reasons could be due to lack of correct local words to convey the information (Adams et al. 2005), or loss of meaning due to use of inadequately trained

interpreters for the purpose or the influence of limited education on the understanding of concepts related to the study (Vasquez and Javier 1991). It has previously been observed that use of investigators who use a language or accent different from that of research participants can affect informed consent comprehension (Escobedo et al. 2007; Musmade 2013). The finding could also imply the need for the development of culturally and linguistically appropriate tools for informed consent comprehension in communities, as advocated by some (Afolabi et al. 2014).

We attributed the low UBACC score seen with the low level of educational attainment to bias that could be shown by such participants to being tested. The task of memory recall could be didactic and embarrassing, a situation that has previously been shown to be a challenge to informed consent comprehension (Sudore et al. 2006).

We noticed some secondary effects during this study for which we did not primarily design it. The use of UBACC led to improvement in the skill and ability of the researcher in the administration of IC to participants during the trial. With time the process became more structured and intuitive leading to prompt completion. It was beneficial especially in emergencies such as when patients presented in cardiac tamponade and time to intervention was crucial in achieving a good outcome. Also, the participants displayed knowledge of the trial concepts and took ownership of the process because of the iterative learning.

Our study was limited by the fact that although the sample size was adequate to test the feasibility of the use of UBACC tool, it was not adequately powered to test for association between identified factors and comprehension. This explains the large confidence interval in the results. Therefore, our findings are mainly exploratory, and we will need to confirm them in a larger similar trial, if not the main IMPI-2 trial, should the pilot trial be positive. Our use of bivariate logistic regression to examine the significance of the association between each baseline characteristics and comprehension at each time point is prone to false significance due to influence of type 1 error. Using longitudinal models like generalized estimating equation or mixed-effect models to examine the impact of these predictors on changes in comprehension

over time is a better method and we intend to use this in subsequent stages of the trial. Secondly, UBACC was conceived to be a screening tool, but in this study, we used it as a teaching tool for improving comprehension of informed consent. Participants with low scores at baseline were not eliminated, whereas in the original UBACC concept, having low scores would have been understood as not having the capacity to consent – again something that could be corrected in the larger trial, also, baseline values were not collected at the same time for everyone.

Another limitation of the study is having the researcher administer the evaluation which could have been a source of bias. The ICC study was conceptualised to improve the dropout rate noticed in the IMPI-2 trial follow-up, however, as shown in the results despite the improvement in participants understanding, many missed their follow-up the longer the trial lasted leading to missing data. This is a potential limitation of the study; however, in the main trial we hope to improve the adherence to follow-up by iterative learning using the UBACC. To report the findings better, we will use of repeated measure anova for the analysis.

Conclusion

The use of an iterative learning tool such as UBACC is feasible in a randomised control trial in Africa and could lead to improved informed consent comprehension among participants. However, it may be better to use trained native language speakers to administer informed consent and evaluate comprehension. There is also a need to develop culturally and linguistically appropriate tools for informed consent comprehension based on local peculiarities.

In the main trial, to better understand the impact of predictors on changes in comprehension over time, we will explore the use of such longitudinal models as mixed-effect regression models and generalised estimating equation in analysing the data.

Table 6.1: Baseline characteristics of the ICC study population

Characteristics	Count (N=7)	Percentage (%)
Age groups (years)		
<20	1	1.4
20-29	10	14.3
30-39	21	30.0
40-49	15	21.4
50-59	11	17.7
60-69	10	14.3
>70	2	2.9
Sex		
Female	32	45.1
Level of Education		
None	4	5.6
Primary†	21	29.6
Secondary	31	43.7
Tertiary	9	12.7
Population group		
South African Blacks‡	48	67.6
Other South Africans§	13	18.3
Foreign Nationals¶	10	14.1
Marital status		
Married	34	47.9
Single	35	49.3
Widow	2	2.8
Previous trial		
No	68	95.8
Yes	3	4.2
Use of Interpreters		
No	47	66.2
Yes	24	33.8

†Grouped with informal education, ‡ Mostly Xhosa, § White and Afrikaans, ¶ Other African Black immigrants
ICC-Informed Consent Comprehension

Table 6.2: Odds of passing UBACC at subsequent visits compared with baseline

Visit	n	Proportion passing (UBACC Score>25)	OR	95% C. I	P (Interaction)
Baseline	64	44.0%			
6 weeks	61	59.0%	1.17	1.01; 1.34	0.033
3 months	50	64.0%	1.28	1.09; 1.46	0.001
6 months	35	69.0%	1.39	1.17; 1.65	<.001

OR-Odd Ratio; C.I- Confidence interval; UBACC- University of California Brief Assessment of Capacity to Consent

Table 6.3: Proportion of passing the UBACC questions at baseline and follow-up

UBACC Questions	**Baseline n= 64**	**6 weeks n=61**	**3 months n=50**	**6 months n=35**
	% Pass	%Pass	% Pass	% Pass
Question 1 What is the purpose of the study that was just described to you?	36%	55%	60%	51%
Question 2 What made you agree to participate in this study?	75%	79%	68%	83%
Question3 Do you believe that this is primarily research or treatment?	53%	57%	54%	74%
Question 4 Do you have to be in this study if you do not want to participate?	78%	85%	84%	80%
Question 5 If you withdraw from this study, will you still be able to receive regular treatment?	58%	57%	58%	74%
Question 6 What are the things you are required to do while in this study?	66%	59%	54%	60%
Question 7 Please mention some of the risk and discomfort that people in this study may experience	45%	41%	42%	37%
Question 8 Please mention the benefits of being in this study	50%	59%	56%	54%
Question 9 Is it possible that the treatment planned in study may not have the expected result?	42%	39%	38%	60%
Question 10 Who will pay for the medical cost if you are injured as a direct result of being in the study?	78%	84%	90%	80%

OR-Odd Ratio; C.I- Confidence interval; UBACC- University of California Brief Assessment of Capacity to Consent

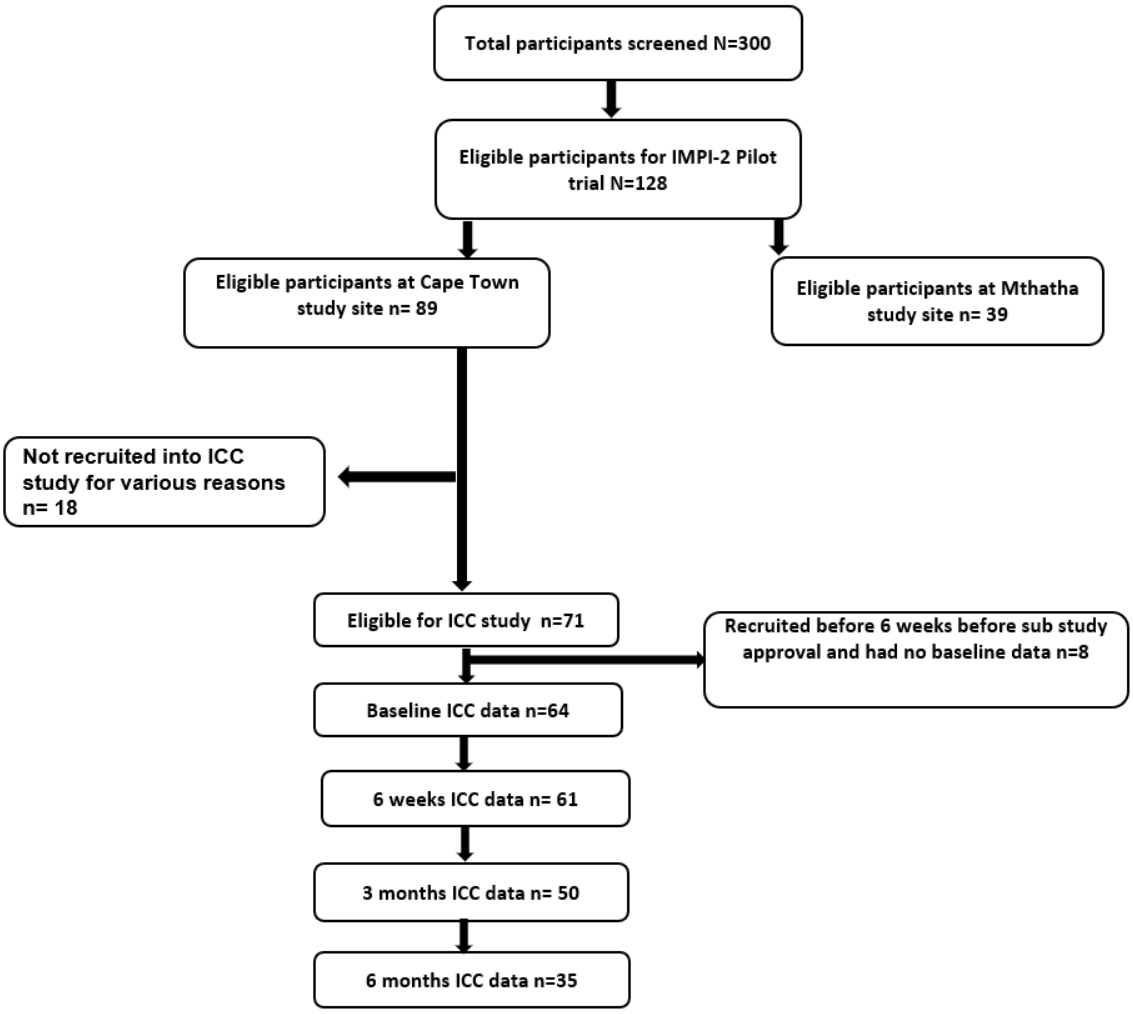

Figure 6.1: The ICC Study Flow *(IMPI- Investigation for management of pericarditis in Africa; UBACC- University of California San Diego Brief Assessment of Capacity to Consent; ICC- Informed consent comprehension)*

Appendix 6.1:

UBACC English Version

No	Question	Score
1	What is the purpose of the study that was just described to you? Response: 3 = To compare between using a drug in the pericardium to facilitate drainage and routine care in patients with pericardial effusion 2= Incorrect answer 1= Don't know or not sure	1 2 3
2	What made you agree to participate in this study? Response: 3 = Find intervention that is best for me, help others 2= Incorrect answer 1= Don't know or not sure	1 2 3
3	Do you believe this is primarily research or primarily treatment? Response: 3 = Both Research and treatment 2= Incorrect answer 1= Don't know or not sure	1 2 3
4	Do you have to be in this study if you do not want to participate? Response: 3 = No I don't have to 2= Incorrect answer 1= Don't know or not sure	1 2 3
5	If you withdraw from this study, will you still be able to receive regular treatment? Response: 3 = Yes 2= Incorrect answer 1= Don't know or not sure	1 2 3
6	What are the things you are required to do while in this study? Response: 3 = At least 2 of the following: Sign consent, answer some question to see if you understood what you signed for, take your medications, come back at weeks 2 and 6, months three, six and twelve for follow up 2= Incorrect answer 1= Don't know or not sure	1 2 3

7	Please mention some of the risk and discomfort that people in this study may experience. Response: 3= At least 2 of the following: the discomfort of the procedure, risk of bleeding, the intervention may not help me, the risk of coming repeatedly to follow up 2= Incorrect answer 1= Don't know or not sure	1 2 3
8	Please mention the benefits of being in this study. Response: 3 = Might learn more about my health, closer follow up, may help the larger society know how to treat the condition better 2= Incorrect answer 1= Don't know or not sure	1 2 3
9	Is it possible that the treatment planned in study may not have the expected result? Response: 3 = Yes, it is possible 2= Incorrect answer 1= Don't know or not sure	1 2 3
10	Who will pay for the medical care cost if you are injured as a direct result of being in the study? Response: 3 = This will be covered by the insurance held at UCT through its no-fault insurance policy which covers the trial 2= Incorrect answer 1= Don't know or not sure	1 2 3
	Total score	

UBACC Xhosa Version

No	Umbuzo	Score
1	Yintoni injongo yesifundo esigqityakucaciswa kuwe? Impendulo: 3=Kukuthelekisa Phakathi kokusebenzisa kwamayeza akwi (pericardium)ekufunxeni incindi ekuxilongeni izigulane ezinoxinezelelo lwe (pericardium) effusion. 2=Yimpendulo engeyiyo 1=Andiyazii okanye andiqinisekanga	1 2 3
2	Yintoni ekwenze ukuba uvume ukuthabatha inxaxheba koluphando? Impendulo: 3 Kukufumana ulwazi olungcono kum, kuzoncedakala nabanye abantu 2=Yimpendulo engeyiyo 1=Andiyazi okanye andiqinisekanga	1 2 3
3	Ingaba ucinga ukuba olu luphando okanye lunyango? Impendulo: 3= Luphando nonyango zombini 2=Yimpendulo engeyiyo 1= Andiyazi okanye andiqinisekanga	1 2 3
4	Ingabo kunyanzelekile na ukuba ube koluphando nokuba awufuni? Impendulo 3 = Hayi andinyanzelekanga 2=Yimpendulo engeyiyo 1=Andazi andiqinisekanga	1 2 3
5	Ukuba uye wayeka ukuthabatha inxaxheba koluphando, ungakwazi ukufumana unyango lwakho njengesiqhelo? Impendulo: 3= Ewe 2=Ympendulo engeyiyo 1=Andiyazi okanye andiqinisekanga	1 2 3
6	Ukuba uthe wathatha inxaxheba koluphando, zeziphi ezinye zezinto ozakucelwa uzenze? Impendulo: 3=Nokuba zimbini kwezi zilandelayo : Ukutyikitya (ukusayina) isivumelwano, uphendule imibuzo ubonisa ukuba uyayiqonda into oyisayineleyo,uthathe amayeza akho ,uphinde ubuye emva kweveki ezimbini ,ezintandathu ,inyanga ezintathu ezintandathu ukuya kunyaka 2= Yimpendulo engeyiyo 1=Andiyazi okanye andiqinisekanga	1 2 3

7	Ndicela uchaze ubungozi okanye ubunzima onokubufumana ukuba uthe wathatha inxaxheba koluphando? Impendulo: 3= Nokuba zimbini kwezi zilandelayo: Ukungahambi kakuhle kwenkqubo leyo uzobe uyenziwa, umngcipheko wokopha, yonke lenkqubo isenokungabiluncedo kum, umngcipheko wokuza ngokuphindelela kutyelelo lwakho. 2=Yimpendulo engeyiyo	1 2 3
	1=Andazi okanye andiqinisekanga	
8	Ndicela uxele inzuzo/amanye amancedo anokufumaneka koluphando? Impendulo: Ndinokufunda lukhulu ngempilo yam, utyelelo olusondeleleneyo,kuncedwe uluntu oluninzi lwazi lukhulu (ncono) ngendlela yolunyango 2= Yimpendulo engeyiyo 1=Andazi okanye andiqinisekanga	1 2 3
9	Ingaba ingenzeka into yokuba oluphando lungangabi luncedo kuwe? Impendulo: 3=Ewe kunokwenzeka. 2=Yimpendulo engeyiyo 1=Andiyazo okanye andiqinisekanga	1 2 3
10	Ngubani ozakuhlawulela unyango lwakho xa uthe walimala usephantsi koluphando? Impendulo: 3= Oko kuyakubazindleko ze inshorensi yase yunivesithi yekapa (UCT) akunamgaqo nkqubo we-inshorensi ejongene noPhando 2=Yimpendulo engeyiyo 1= Andiyazi okanye andiqinisekanga	1 2 3
	Uvavanyo lokuqala Uvavanyo lwesibini Uvavanyo lwesithathu	
	Amanqaku eziphumo	

UBACC Afrikaan's Version

No	Question	Score
1	Wat is die doel van die studie wat vir u beskryf was? Antwoord. 3 = Om te vergelyk tussen 'n drogeiy/medisyne wat in die perikardium gespuit word of routine behandeling. Om dreinering te verbeter in patiente met perikardiale effusie. 2=verkeerde antwoord 1=ek weet nie	1 2 3
2	Hoekam sal jy dit oorweeg om aan die studie deel te neem. Antwoord 1= Om beste behandeling vir my te kry en ook sodoente andere te help 2=verkeerde antwoord 3=Weet nie, nie seker	1 2 3
3	Glo jy dit is eerstens navorsing of primere behandeling Antwood: 3= altwee Navorsing en Behandeling 2=Verkeerde antwoord 1=Weet nie ;nie seker	1 2 3
4	Moet jy in die studie wees al wil jy nie deelneem nie Antwoord 3=Nee ek hoef nie 2=Verkeerde antwoord 1= Weet nie; nie seker nie	1 2 3
5	Indien jy onttrek van die studie,sal jy nog steeds dieselfde behandeling kry Antwood: 3=Ja 2=Verkeerde antwoord 1=Weet nie;nie seker nie	1 2 3
6	Indien jy deelneem aan die studie is daar sommige goed wat van jou verwag sal word. Antwoord: 3= Ten minste (2) twee van die volgende (i) toestemming te teken (ii) sommige vrae te beentwoord om te sien of jy verstaan waarvoor jy teken (iii) Medisyne te neem soos voorgeskryf. (iv)die kliniek by te woon op 2weke;6weke;3maande;6maande en 1jaar. 2= Verkeerde antwoord 1= Nie seker;weet nie	1 2 3

7	Beskryf sommige risikos of ongemak patiente kan ondervind indien hulle aan die studie deelneen Antwoord 3=ten minste 2 van die volgende; (i) Die ongemak van die procedure (ii) Risiko van bloeding (iii) Die intervensie mag nie help nie (iv) Die ongerief om gereeld die kliniek by te woon	1 2 3
8	Beskryf sommige voordele van die studie? Antwoord: 3= Mag meer leer van my gesondheid;gereelde opvolg Mag die groote gemeenskap help met beter behandeling. 2=verkeerde antwoord 1=weet nie ;nie seker nie	1 2 3
9	Is dit moonthlik dat hierdie studie geen vooideel vir jou inhou nie ? Antwood: 3= Ja 2=verkeerde antwoord 1=Weet nie;nie seker nie	1 2 3
10	Wie sal betaal vii mediese sorg? Indien jy beseer word as direkte oorsaak van die deelname aan die studie. Antwooid 3= Die assuransie van UCT sal betaal deur die geen skuld assuransie polis wat die studie dek. 2=Verkeerde antwoord 1=Weet nie;nie seker nie	1 2 3
	Totale Puntetelling	
	Evaluasie 1 Evaluasie 2 Evaluasie 3	

Appendix 6.2: Sample size calculation table for estimating the proportion of patients who will accept UBACC evaluation using a 95% confidence interval for different values of the margin of error (E) and prior estimate (P)

	Prior estimate (P)									
	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95
E	0.01	9604	9507	9219	8739	8067	7203	6147	4898	3457	1824
	0.05	384	372	368	349	322	288	245	195	138	73
	0.10	96	95	92	87	80	72	61	49	34	18

P = prior estimate of the proportion of eligible patients that would accept UBACC evaluation

E= Margin of error of estimate

Sample size (n) = 1.96^2*P(1-P)/E^2

Appendix 6.3: ICC study analysis plan

Objective	Outcome	Explanatory variable if applicable	Criteria for feasibility/ hypothesis	Method of analysis
Primary feasibility: To determine the feasibility of using the UBACC as training tool in improving and evaluating comprehension of the IC process among participants in a clinical	Acceptance of use of tool, measured as percentage of patients who agree to using the tool to evaluate the comprehension of the IC process	N/A	Criteria for success of feasibility: At least 50% of eligible trial patients will accept the evaluation	Descriptive statistics expressed as percentage (95% confidence interval)
Secondary feasibility objectives: 1. If the biological intervention in the form of using UBACC as an educational tool improves the response	UBACC score of ≥25	Time: comparing baseline performance with 6 weeks, 3 months and 6 months	IC comprehension will improve over time	Logistics regression
2. Determine if there are factors associated with response	UBACC score of ≥25	• Sex • Age • Educational level • Use of interpreters • Language of administration of UBACC	Sex, age Low level of education, use of interpreters and not administering the IC in English Language will be associated with comprehension.	Logistics regression

Appendix 6.4: Progression of consent comprehension with Follow-up

(UBACC- University of California Brief Assessment of Capacity to Consent)

Appendix 6.5**:** Bivariate model showing the odds of different variables in relation to UBACC score with Follow-up

	Baseline			6 weeks			3 months			6 months		
	OR	**95% C. I**	**p value**	**OR**	**95% C. I**	**p value**	**OR**	**95% C. I**	**p value**	**OR**	**95% C. I**	**p value**
Sex[†]												
Female	0.42	0.15;1.19	0.10	0.29	0.10-0.85	0.03	0.42	0.13-1.37	0.15	0.48	011-2.10	0.33
Education [‡]												
Secondary	1.20	0.40-3.59	0.74	2.00	0.65-6.19	0.23	9.17	2.11-39.8	0.00	1.78	0.32-10.0	0.51
Origin[¶]												
Xhosa	2.43	0.57-10.4	0.23	0.89	0.21-3.62	0.86	1.53	0.34-6.87	0.58	1.71	0.23-12.6	0.59
Foreign nationals	2.13	0.33-13.8	0.43	1.33	0.20-8.17	0.76	1.60	0.24-10.8	0.63	1.00	0.08-12.6	1.00
Use of Interpreter[#]												
Yes	0.34	0.11-1.04	0.06	0.42	0.14-1.26	0.12	0.42	0.12-1.42	0.162	1.75	0.40-7.58	0.45

OR- Odd Ratio; C.I- Confidence Interval ICC-Informed Consent Comprehension
†Female compared to male, [‡] Secondary level and above compared to Primary level and below, [¶] Afrikaans not shown,
[#]compared to without an interpreter

Appendix 6.6: UBACC scores over the study period

UBACC Questions	Baseline	6 weeks				3 months				6 months			
	%Pass	%Pass	OR	95% CI	P value	%Pass	OR	95% CI	P value	%Pass	OR	95% CI	P value
Question 1 What is the purpose of the study that was just described to you?	36%	51%	1.15	0.99; 1.33	0.061	60%	1.27	1.08; 1.48	0.003	51%	1.20	1.01; 1.43	0.044
Question 2 What made you want to consider participating in this study?	75%	79%	1.05	0.92; 1.19	0.493	68%	0.96	0.84; 1.10	0.538	83%	1.16	0.99; 1.35	0.059
Question 3 Do you believe this is primarily research or primarily treatment?	53%	57%	1.05	0.92; 1.20	0.447	54%	1.05	0.92; 1.21	0.458	74%	1.35	1.15; 1.59	<0.001
Question 4: Do you have to be in this study if you do not want to participate?	78%	85%	1.07	0.96; 1.20	0.219	84%	1.06	0.94; 1.20	0.303	80%	1.05	0.92; 1.20	0.475
Question 5: If you withdraw from this study, will you still be able to receive regular treatment?	58%	57%	0.94	0.82; 1.08	0.395	58%	1.01	0.87;1.17	0.930	74%	1.23	1.04; 1.45	0.016
Question 6: If you participate in this study, what are some of the things you will be asked to do?	66%	59%	0.94	0.80; 1.10	0.426	54%	0.88	0.74; 1.04	0.131	60%	0.94	0.78; 1.14	0.533
Question 7: Please describe some of the risk or discomfort that people may experience if they participate in this study	45%	41%	0.94	0.81; 1.09	0.429	42%	0.94	0.81; 1.11	0.477	37%	0.89	0.74; 1.06	0.201
Question 8: Please describe some of the benefits of this study.	50%	59%	1.09	0.94; 1.27	0.242	56%	1.06	0.90; 1.24	0.508	54%	1.02	0.85; 1.22	0.855
Question 9: Is it possible that the study drug may not have any benefit?	42%	39%	0.97	0.83; 1.14	0.732	38%	0.96	0.82; 1.14	0.663	60%	1.19	0.99; 1.44	0.069
Question 10: Who will pay for medical care if you are injured as a direct result of participating in this study?	78%	84%	1.05	0.93; 1.19	0.400	90%	1.13	0.99; 1.28	0.077	80%	1.01	0.87; 1.18	0.850

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CHAPTER SEVEN
CONCLUSIONS

"*A wise man is not one that gives correct answers, but rather the one that poses the right questions because the wise learn much more from foolish questions than the fool from wise answers*" African Proverb

This thesis began by ruminating over an old African proverb from the Ashanti people in Ghana, that "*you do not test the depth of a river with both feet*". The central theme was on how smaller studies lead to larger ones. Each chapter of the thesis dwelt on one aspect of asking a scientific question, coalescing in the pilot trial of the second investigation of the management of pericarditis in Africa (IMPI-2 Trial).

The IMPI project brings to fore the maxim that local challenges are only better tackled with homemade solutions. Pericarditis, the focus of the IMPI trial, is a common cause of cardiac morbidity and mortality. However, the peculiarities in Africa and most of the low- and medium-income countries make tuberculosis a prominent cause of pericarditis, a situation that has not been made any better by the scourge of human immunodeficiency virus. It is for this reason that the thesis devoted a prominent part of the introduction on tuberculous pericarditis. Pilot trials a fundamental concept in raising, refining and trying scientific research questions, formed the foundation for the subsequent chapters by arming our understanding going into the IMPI-2 pilot trial.

Several factors make it very challenging to conduct and complete large, expensive randomised control trials in Africa and most resource-limited settings. Some of these include readiness and capacity of the centres to undertake the processes, funders confidence, the cooperation of the physicians to refer potential participants, patients understanding of the trail information and commitment to follow-up.

Pilot studies are essentials tools as the first step in the conduct of large RCT, and if correctly done, they could help in providing the solution to most of the challenges above and thus set the stage for definitive trials. The thesis uses Investigation of Management of Pericarditis (IMPI) trials to explore

and describe the potential use of pilot studies and subgroup analyses in limited resource environments. It uses the pilot phase of the IMPI-2, to describes practical challenges and lessons learned which will prepare the IMPI-2 investigators for the main phase of randomised controlled trial.

The Strengths/Merit of this Work

There were several fundamental lessons learned from performing the research for this thesis:

1. Inadequate reporting of pilot trials identified by critical appraisal of the literature can lead to loss of valuable information emanating from randomised control trials. To mitigate against this, it is imperative that one insists on complete and thorough reporting with the aid of checklist such as the Consolidated Standards of Reporting Trials (CONSORT).
2. Subgroup analysis is an essential statistical tool that can be used to effectively and reliably answer critical clinical questions which may be glossed over in large RCTs and thus obviate the need to conduct another expensive and resource intensive clinical trials.
3. There is a vast difference between planning and implementation in clinical trials. In the conduct of clinical studies, it is essential to ensure the smooth running of all the processes. The IMPI-2 pilot study allowed for the ascertaining of such parameters as data collection tools, potential recruitment sites, measures of outcome and protocol needed several changes during the pilot trial. Though these steps were daunting, therein lay the beauty of a pilot trial, as we learnt in the IMPI-2 trial. Our result showed that randomised control trial of patients with large pericardial effusion was feasible based on our recruitment rate; however, this was not without challenges and required several meetings, re-strategizing and adjustments. A good percentage of the study population was between 39-59 years, these are the core of workforce for any nation, and a sad reminder to the horrifying impact of diseases such as tuberculosis and HIV/AIDS on the economic development of Africa.
4. Reducing attrition is essential in achieving success in a trial. We saw this as a significant challenge in the successful conduct of IMPI-2 trial. Ensuring informed consent comprehension, we learnt could improve follow-up. The Informed Consent Comprehension Study presented in chapter six first showed that it was feasible to use tools such as UBACC

to evaluate consent comprehension in the context of clinical trials in Africa. Its use also assisted in gaining the confidence of trial participants in the trial process, leading to improvement in adherence to follow-up. There was also a subjective improvement in informed consent delivery skills of the researcher. These effects will require more solid confirmation in future trials.

Implications of outcomes of the thesis for future research in low- and middle-income countries

The findings in this thesis lead us to recommend that in resource-limited settings, researchers and clinical trialists should explore using pilot studies, subgroup analyses, more thorough critical appraisal of the literature, as effective means of preparation for trial, answering important questions and getting clinical results before conducting the main study.

The concepts discussed in this thesis serves as veritable tools in the planning of future trials as it highlights significant areas such as the impact on the design, conduct, analysis and presentation of main studies. It explores and describes the potential use of pilot studies and subgroup analyses in resource-limited environments.

The findings of IMPI-1 trial on use of corticosteroids in tuberculous pericarditis continue to shape clinical management in this disease. The implication of the subgroup analysis presented in chapter 4 may infact be that amongst patients presenting with effusive pericarditis, evidence of hemodynamic instability who are unwell, while corticosteroids may not be needed in those who undergo pericardiocentesis, the same may not be true who are unable to receive the procedure. This finding also provides an important knowledge gap about 1) the optimal management of patients who are unable to access pericardiocentesis and the potential role of corticosteroids and 2) the potential impact of role routine complete pericardiocentesis compared to usual care in pericardial effusion. The IMPI-2 trial is set to provide part of the answer to this later question. The preliminary findings of the

initial phase of the pilot as presented in chapter five of the thesis will help prepare the IMPI-2 investigators and others to be able to conduct a large simple randomised controlled trial effectively.

Limitations of the thesis

Several challenges delayed the commencement and completion of the pilot trial. These contributed to the prolongation of the duration of the pilot study and non-commencement of the main. It was a limitation in the thesis as ideally one would have loved to practically see the impact of the pilot study on the main trial processes.

During the conceptualisation of the IMPI-2 feasibility study, 218 participants were calculated as the required internal pilot study population to inform the commencement of the main trial. However, the pilot report presented in this thesis used 130 participants. At the planning stage, 11 sites were to be involved in the recruitment for the pilot; this was later reduced to eight locations. However, only two study sites participated in the pilot study for the 16-18 months covered by the report due to logistical challenges. As a result, the robust experience that would have accrued from a multi-centre pilot study was lost resulting also in a low study population. These were significant limitations.

Also, we noted a high drop-out rate during follow-up, and the informed consent comprehension (ICC) substudy presented in **chapter six** was a response to this.

Despite the noble intentions, the findings of the ICC study would have been more objective if trained interviewers were engaged to conduct the interviews rather than the clinical researcher. Not doing so could have been a source of bias, as already alluded to in chapter six. Use of the tool also was not formerly part of the IMPI-2 pilot trial, and it could not, therefore, be administered on all participants, thus limiting its conclusions. Also, the original intended use of the tool for screening was different from its current use for teaching and evaluation of consent comprehension.

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